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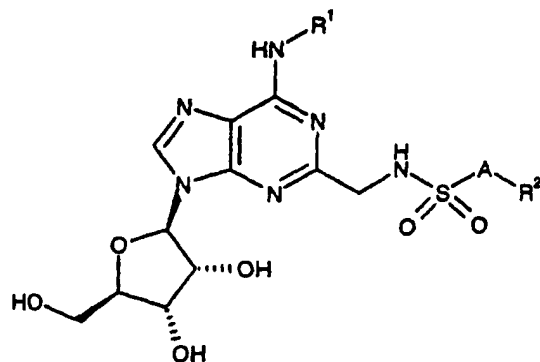
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(54) Title: PURINE DERIVATIVES



(I)

(57) Abstract: The present invention relates to compounds of the formula (I) and pharmaceutically acceptable salts and solvates thereof, to processes for the preparation of, intermediates used in the preparation of, and compositions containing such compounds and the uses of such compounds as adenosine A2a receptor agonists.

WO 01/27130 A1

PURINE DERIVATIVES

This invention relates to purine derivatives. More particularly, this invention relates to N-[(purin-2-yl)methyl]sulphonamide derivatives and to processes for
5 the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

These derivatives are selective, functional agonists of the human adenosine A2a receptor and may be used as anti-inflammatory agents in the treatment of,
10 *inter alia*, diseases of the respiratory tract.

Adenosine is a ubiquitous molecule having a central role in mammalian intermediary metabolism. Independently, adenosine acts on multiple surface receptors to produce a variety of responses. Adenosine receptor classification
15 has revealed the presence of at least four subtypes: A1, A2a, A2b and A3. Stimulation of adenosine A2 receptors on the surface of human neutrophils has been reported to potently inhibit a range of neutrophil functions. Activated neutrophils can damage lung tissue by release of reactive oxygen species, for example, superoxide anion radicals ($O_2^{\cdot-}$), and granule products, for example,
20 human neutrophil elastase (HNE), amongst other inflammatory mediators. In addition, activated neutrophils perform both *de novo* synthesis and release of arachidonate products such as leukotriene B₄ (LTB₄). LTB₄ is a potent chemo-attractant that recruits additional neutrophils to the inflammatory focus, whereas released $O_2^{\cdot-}$ and HNE adversely affect the pulmonary extracellular matrix. The
25 A2 receptor subtype mediating many of these responses ($O_2^{\cdot-}$ and LTB₄/HNE release and cell adhesion) is established as A2a. The A2 subtype (A2a or A2b) mediating the other effects remains to be established.

Selective agonist activity at the A2a receptor is considered to offer greater
30 therapeutic benefit than the use of non-selective adenosine receptor agonists because interaction with other subtypes is associated with detrimental effects in the lung in animal models and human tissue studies. For example, asthmatics,

but not non-asthmatics, bronchoconstrict when challenged with inhaled adenosine. This response is at least in part due to the activation of the A1 receptor subtype. Activation of A1 receptors also promotes neutrophil chemotaxis and adherence to endothelial cells, thus promoting lung injury.

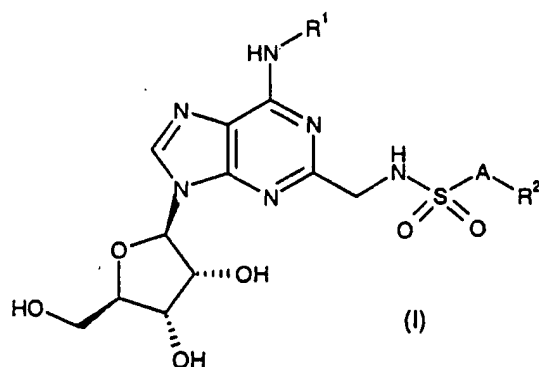
- 5 Furthermore, many patients with respiratory disease will be co-prescribed β_2 -agonists, and negative interaction has been shown in animal studies between isoprenaline and adenosine receptors negatively coupled to adenylate cyclase. Degranulation of human mast cells is promoted by activation of adenosine A2b receptors, thus selectivity over the A2b receptor is also advantageous.

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- We have now surprisingly found the present purine derivatives inhibit neutrophil function and are selective agonists of the adenosine A2a receptor. They may also have antagonist activity at the adenosine A3 receptor. The present compounds may be used to treat any disease for which an adenosine A2a
- 15 receptor agonist is indicated. They can be used to treat a disease where leukocyte (e.g. neutrophil, eosinophil, basophil, lymphocyte, macrophage) - induced tissue damage is implicated. They are useful as anti-inflammatory agents in the treatment of diseases of the respiratory tract such as adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic
- 20 obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis. The present compounds may also be used in the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple
- 25 sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori* gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing.

30

Accordingly, the present invention provides a compound of the formula:



5

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is hydrogen or C_1 - C_6 alkyl optionally substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl, said phenyl and naphthyl
10 being optionally substituted by C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo or cyano;

A is a bond or C_1 - C_3 alkylene;

R^2 is (i) hydrogen, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, phenyl or naphthyl, said C_3 - C_7
15 cycloalkyl, phenyl or naphthyl being optionally substituted by C_1 - C_6 alkyl, phenyl, C_1 - C_6 alkoxy-(C_1 - C_6)-alkyl, R^3R^3N -(C_1 - C_6)-alkyl, fluoro-(C_1 - C_6)-alkyl, fluoro-(C_1 - C_6)-alkoxy, C_2 - C_5 alkanoyl, halo, $-OR^3$, cyano, $-COOR^3$, C_3 - C_7 cycloalkyl, $-S(O)_mR^4$, $-NR^3R^3$, $-SO_2NR^3R^3$, $-CONR^3R^3$, $-NR^3COR^4$ or $-NR^3SO_2R^4$, with the proviso that R^2 is not hydrogen when A is a bond,
20 or (ii) when A is C_2 - C_3 alkylene, $-NR^7R^8$, $-OR^3$, $-COOR^3$, $-OCOR^4$, $-SO_2R^4$, $-CN$, $-SO_2NR^3R^3$, $-NR^3COR^4$ or $-CONR^3R^3$,
or (iii) a C-linked, 4 to 11 membered, mono or bicyclic heterocycle having either from 1 to 4 ring nitrogen atom(s) or 1 or 2 nitrogen and 1 oxygen or 1 sulphur ring atoms, optionally C-substituted by oxo, C_1 - C_6 alkoxy-(C_1 - C_6)-alkyl,
25 R^3R^3N -(C_1 - C_6)-alkyl, fluoro-(C_1 - C_6)-alkyl, fluoro-(C_1 - C_6)-alkoxy, fluoro-(C_2 - C_5)-alkanoyl, halo, cyano, $-OR^5$, R^6 , $-COR^5$, $-NR^5R^5$, $-COOR^5$, $-S(O)_mR^6$,

-SO₂NR⁵R⁵, -CONR⁵R⁵, -NR⁵SO₂R⁶ or -NR⁵COR⁶ and optionally N-substituted by C₁-C₆ alkoxy-(C₁-C₆)-alkyl, R³R³N-(C₂-C₆)-alkyl, fluoro-(C₁-C₆)-alkyl, fluoro-(C₂-C₅)-alkanoyl, R⁶, -COR⁵, -COOR⁵, -S(O)_mR⁶, -SO₂NR⁵R⁵ or -CONR⁵R⁵;

5

R³ is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl or phenyl;

R⁴ is C₁-C₆ alkyl, C₃-C₇ cycloalkyl or phenyl;

10

R⁵ is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl, naphthyl or het;

15 R⁶ is C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl, naphthyl or het;

either, R⁷ and R⁸, taken together with the nitrogen atom to which they are attached represent azetidiny, pyrrolidiny, piperidiny, morpholinyl, piperazinyl, 20 homopiperidiny, homopiperazinyl or tetrahydroisoquinolinyl, each being optionally substituted on a ring carbon atom by C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl, C₁-C₆ alkoxy-(C₁-C₆)-alkyl, R³R³N-(C₁-C₆)-alkyl, fluoro-(C₁-C₆)-alkyl, -CONR³R³, -COOR³ or C₂-C₅ alkanoyl; and optionally substituted on a ring carbon atom not adjacent to a ring nitrogen atom by fluoro-(C₁-C₆)-alkoxy, halo, 25 -OR³, cyano, -S(O)_mR⁴, -NR³R³, -SO₂NR³R³, -NR³COR⁴ or -NR³SO₂R⁴, and said piperazin-1-yl and homopiperazin-1-yl being optionally substituted on the ring nitrogen atom not attached to A by C₁-C₆ alkyl, phenyl, C₁-C₆ alkoxy-(C₂-C₆)-alkyl, R³R³N-(C₂-C₆)-alkyl, fluoro-(C₁-C₆)-alkyl, C₂-C₅ alkanoyl, -COOR⁴, C₃-C₈ cycloalkyl, -SO₂R⁴, -SO₂NR³R³ or -CONR³R³,

30

or, R^7 is H, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, phenyl or benzyl and R^8 is H, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, phenyl, benzyl, fluoro- $(C_1$ - $C_6)$ -alkyl, $-\text{CONR}^3\text{R}^3$, $-\text{COOR}^4$, C_2 - C_5 alkanoyl or $-\text{SO}_2\text{NR}^3\text{R}^3$;

5

m is 0, 1 or 2; and

"het", used in the definitions of R^5 and R^6 , means C-linked pyrrolyl, imidazolyl, triazolyl, thienyl, furyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, 10 pyrimidinyl, pyridazinyl, pyrazinyl, quinolinyl, isoquinolinyl, benzimidazolyl, quinazolinyl, phthalazinyl, benzoxazolyl or quinoxalinyl, each optionally substituted by C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cyano or halo.

In the above definitions, halo means fluoro, chloro, bromo or iodo and alkyl, 15 alkylene, alkanoyl and alkoxy groups containing the requisite number of carbon atoms can be unbranched or branched chain. The heterocycle as defined in R^2 , part (iii), above may be aromatic or fully or partially saturated. The expression 'C-linked' used in the definition of R^2 and "het" means that the group is linked to the adjacent atom by a ring carbon atom. Examples of alkyl include methyl, 20 ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of alkylene include methylene, 1,1-ethylene, 1,2-ethylene, 1,3-propylene and 1,2-propylene. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

25

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts 30 and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate,

fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, *p*-toluenesulphonate and pamoate salts.

- 5 Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

For a review on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19 (1977).

10

The pharmaceutically acceptable solvates of the compounds of the formula (I) include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) are

- 15 polymorphs thereof.

A compound of the formula (I) may contain one or more additional asymmetric carbon atoms and therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the

- 20 formula (I) together with mixtures thereof.

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or

25 derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically

- 30 active acid or base, as appropriate.

Preferably, R^1 is C_1 - C_6 alkyl optionally substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl.

Preferably, R^1 is C_1 - C_6 alkyl substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl.

- 5 Preferably, R^1 is C_1 - C_4 alkyl substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl.

Preferably, R^1 is C_1 - C_2 alkyl substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl.

Preferably, R^1 is phenylethyl, diphenylethyl or naphthylmethyl.

- 10 Preferably, R^1 is 2-phenylethyl, 2,2-diphenylethyl or 1-naphthylmethyl.

Preferably, A is a bond.

Preferably, A is C_1 - C_3 alkylene.

Preferably, A is C_2 - C_3 alkylene.

Preferably, A is C_2 alkylene.

- 15 Preferably, A is $-CH_2CH_2-$.

Preferably, R^2 is C_1 - C_6 alkyl, phenyl or NR^7R^8 .

Preferably, R^2 is 2-methylprop-1-yl, phenyl or NR^7R^8 .

Preferably, $-A-R^2$ is 2-methylprop-1-yl, phenyl or $-CH_2CH_2NR^7R^8$.

Preferably, R^7 is C_1 - C_6 alkyl.

- 20 Preferably, R^7 is C_1 - C_3 alkyl.

Preferably, R^7 is propyl.

Preferably, R^7 is prop-2-yl.

Preferably, R^8 is C_3 - C_8 cycloalkyl.

Preferably, R^8 is C_3 - C_6 cycloalkyl.

- 25 Preferably, R^8 is cyclopentyl.

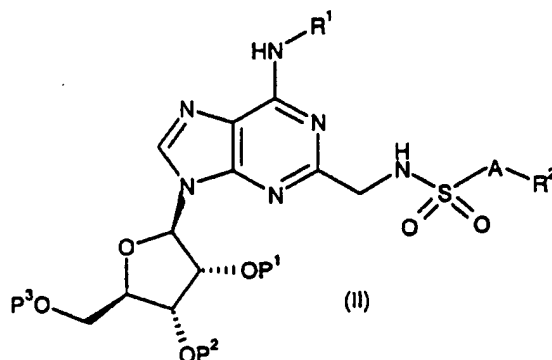
Preferred heterocycles included in the definition of R^2 , part (iii) are pyrrolyl, imidazolyl, triazolyl, thienyl, furyl, thiazolyl, oxazolyl; thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, quinolinyl, isoquinolinyl, benzimidazolyl, quinazolinyl, phthalazinyl, benzoxazolyl, quinoxalinyl, 1,2-
5 dihydroisoquinolinyl, 3,4-dihydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, azetidiny, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl and piperazinyl.

Preferred examples of compounds of the formula (I) include those of the
10 Examples section hereafter, including any pharmaceutically acceptable salts thereof.

The compounds of the formula (I) can be prepared by conventional routes such as by the procedures described in the general methods presented below or by
15 the specific methods described in the Examples section, or by similar methods thereto. The present invention also encompasses these processes for preparing the compounds of formula (I), in addition to any novel intermediates used therein. In the general methods described, R^1 , R^2 and A are as previously defined unless otherwise stated.

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All the compounds of formula (I) may be prepared by the deprotection of a compound of formula

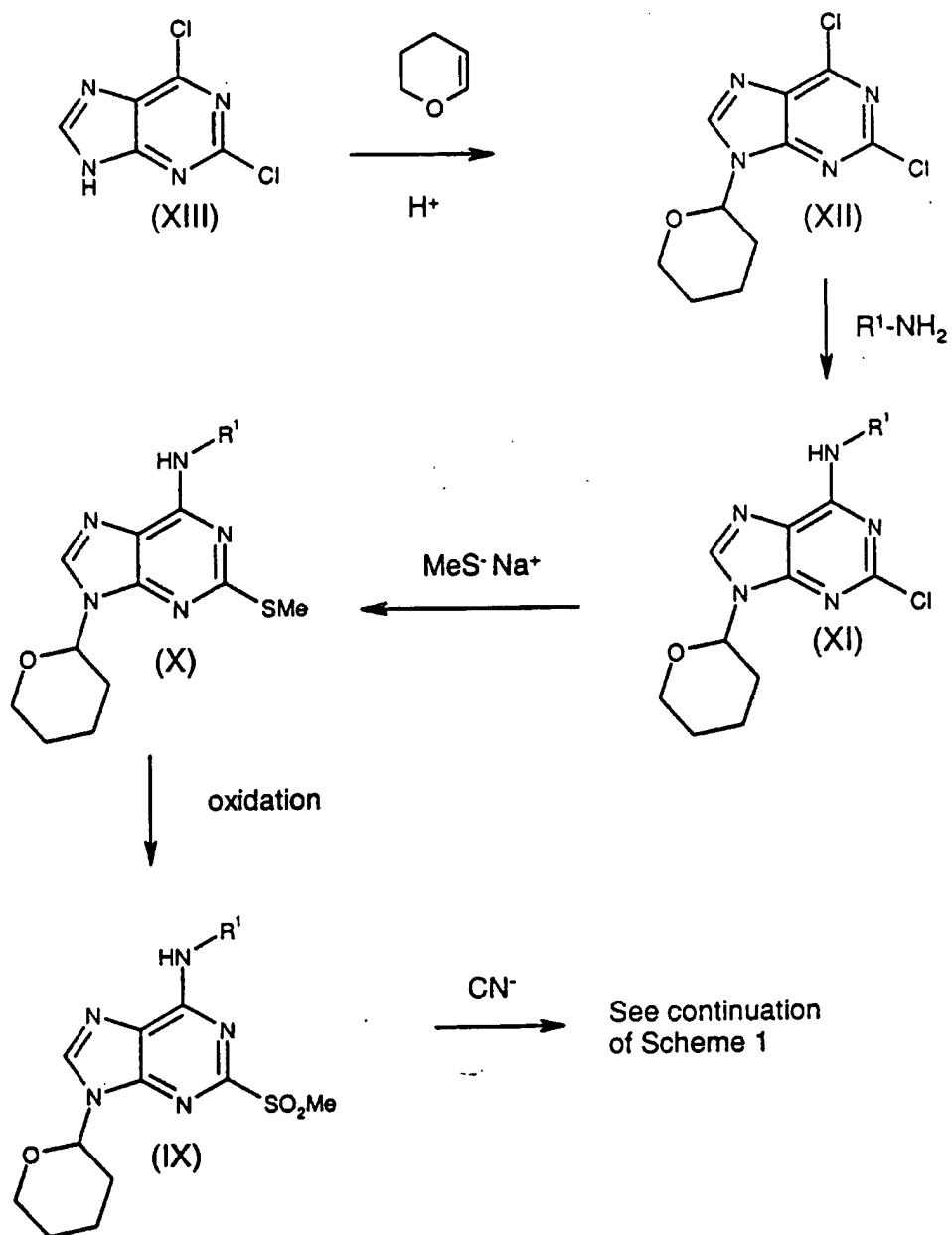


wherein P^1 , P^2 and P^3 represent suitable protecting groups which may be the same or different or P^1 and P^2 optionally form part of the same protecting group. Examples of suitable protecting groups will be apparent to the skilled person [see for instance 'Protecting Groups in Organic Synthesis (Second Edition)',
5 Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. Preferred individual protecting groups are silyl (substituted with three groups independently selected from aryl and alkyl), alkanoyl and aroyl. A preferred protecting group where P^1 and P^2 form part of the same protecting group is where P^1 and P^2 taken together are C_1 - C_6 alkylene. Particularly preferred
10 individual protecting groups are acetyl and benzoyl. Suitable conditions for the deprotection are well known in the art [see for instance 'Protecting Groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical procedure, where P^1 , P^2 and P^3 are each acetyl, the protecting groups may be removed by treating a solution of
15 the compound of formula (II) in a suitable solvent, such as a mixture of water and methanol, with a base such as sodium carbonate, typically at room temperature.

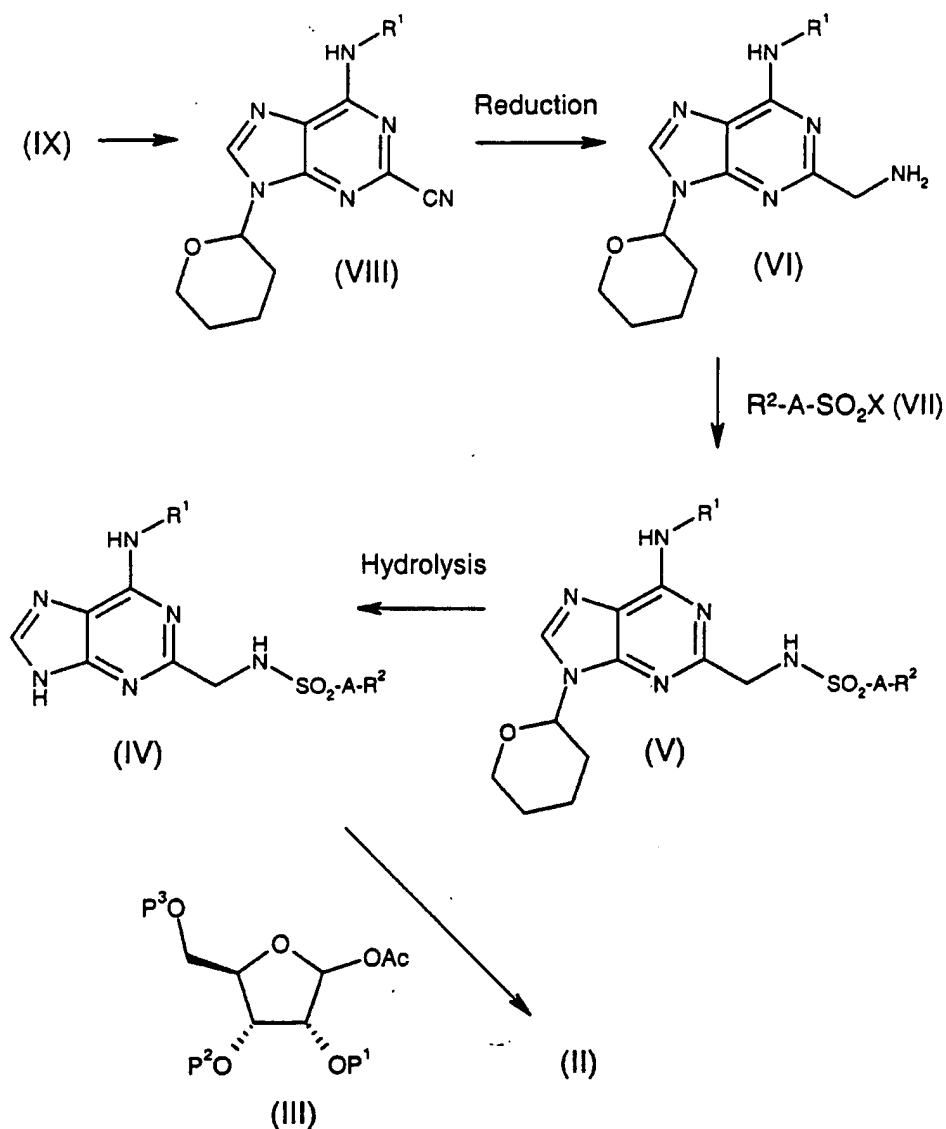
The protecting groups P^1 , P^2 and P^3 may be removed together in a single step
20 or sequentially, in any order. Alternatively, any two of the protecting groups P^1 , P^2 and P^3 may be removed together in a single step and the remaining group may be removed in a separate step, in either order.

The compounds of formula (II) may be prepared according to the routes shown
25 in Schemes 1 and 2, in which X is a leaving group, preferably chloro and P^1 , P^2 and P^3 are as defined above.

Scheme 1



Scheme 1 (continued)



In Scheme 1, compounds of the formula (II) may be prepared by the reaction of
5 a compound of the formula (III) with a compound of the formula (IV) according
to known methods. In a typical procedure, the compound of the formula (III) is
heated with N,O-bis(trimethylacetamide) in an inert solvent such as 1,1,1-
trichloroethane, the solvent is removed and a solution of the residue, in a
suitable solvent such as toluene, is heated, preferably under reflux, with the

compound of the formula (IV) and trimethylsilyltriflate. Compounds of the formula (IV) may be prepared by the hydrolysis of a compound of the formula (V). Typically, the compound of the formula (V) is dissolved in a suitable solvent, such as ethanol, and treated with an acid such as hydrochloric acid.

5 The reaction is preferably performed from 0 to 100 °C, most preferably from 20 to 50 °C. Compounds of the formula (V) may be prepared by the sulphonylation of a compound of the formula (VI) with a compound of the formula (VII). In a typical procedure, a solution of the compound of the formula (VI) in a suitable inert solvent such as dichloromethane is treated with the compound of the

10 formula (VII). An acid acceptor such as triethylamine may optionally be added. Compounds of the formula (VI) may be prepared by the reduction of a compound of the formula (VIII). The reduction may be carried out with any suitable hydride reducing agent or by hydrogenation. In a typical procedure, a solution of the compound of the formula (VIII) in a suitable solvent such as

15 ethanol is saturated with ammonia gas, treated with an appropriate hydrogenation catalyst such as Pearlmann's catalyst and pressurised with hydrogen, preferably to about 414 kPa (60 psi). Compounds of the formula (VIII) may be prepared by reacting a compound of the formula (IX) with a source of cyanide anion such as potassium cyanide. The reaction is typically

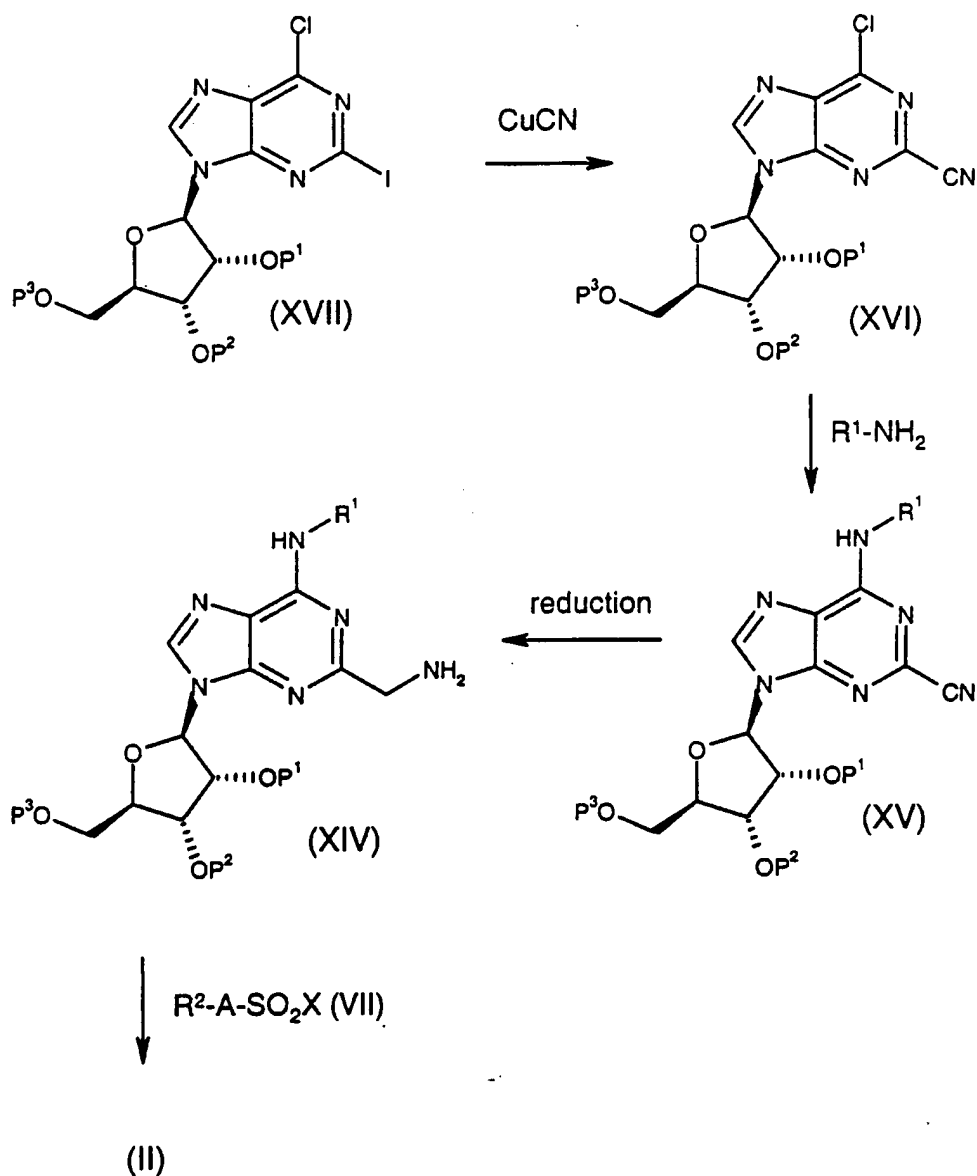
20 carried out in a solvent such as N,N-dimethylformamide at an elevated temperature. Compounds of the formula (IX) may be prepared by the oxidation of a compound of the formula (X). In a typical procedure, an aqueous solution of potassium peroxymonosulphate is added to a solution of the compound of the formula (X) and sodium hydrogencarbonate in a suitable solvent, such as a

25 mixture of water and acetone. Compounds of the formula (X) may be prepared by the displacement of chloride in a compound of the formula (XI) with thiomethoxide. Typically, the reaction is carried out in a polar solvent such as N,N-dimethylformamide, at elevated temperatures and under an atmosphere of nitrogen. Thiomethoxide is used as an alkali metal salt such as sodium

30 thiomethoxide. Compounds of the formula (XI) may be prepared by the reaction of a compound of the formula (XII) with an appropriate primary amine. Typically, a solution of the dichloropurine (XII) in a solvent such as isopropyl

alcohol is treated with the amine and heated under reflux. An additional acid acceptor such as diphenylethylamine may optionally be added. Compound (XII) may be prepared by the reaction of 2,6-dichloro-9*H*-purine (XIII) with dihydropyran in a suitable solvent such as ethyl acetate and in the presence of
5 an acid catalyst such as 4-toluenesulphonic acid, usually at an elevated temperature.

Scheme 2



In Scheme 2, compounds of the formula (II) may be prepared by the
5 sulphonylation of a compound of the formula (XIV) with a compound of the
 formula (VII). In a typical procedure, a solution of the compound of the formula
 (XIV) in a suitable inert solvent such as dichloromethane is treated with the
 compound of the formula (VII). An acid acceptor such as triethylamine may be
 optionally added. Compounds of the formula (XIV) may be prepared by the
10 reduction of a compound of the formula (XV). The reduction may be carried out

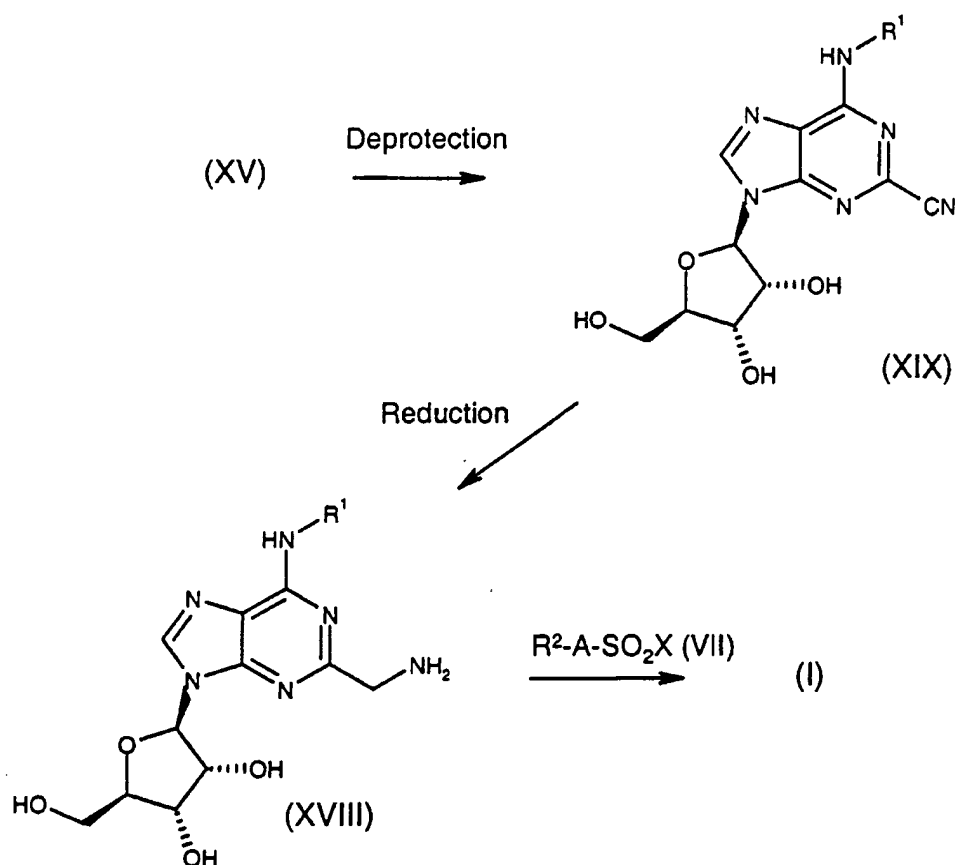
with any suitable hydride reducing agent or by hydrogenation. In a typical procedure, a solution of the compound of the formula (XV) in a suitable solvent, such as ethanol, is saturated with ammonia gas, treated with an appropriate hydrogenation catalyst such as 5% w/w palladium on charcoal and pressurised
5 with hydrogen, preferably to 1034 kPa (150 psi). Compounds of the formula (XV) may be prepared by the reaction of a compound of the formula (XVI) with an appropriate primary amine. Typically, a solution of the compound (XVI) in a suitable solvent such as acetonitrile is treated with the amine at room temperature. An additional acid acceptor such as diphenylethylamine may
10 optionally be added. Compounds of the formula (XVI) may be prepared by the substitution of the iodo group in a compound of the formula (XVII) with cyanide. Typically, a solution of the compound of the formula (XVII) in a suitable solvent (e.g. N,N-dimethylformamide) is treated with copper(II)cyanide and heated, preferably at a temperature in excess of 100 °C. Compounds of the formula
15 (XVII) are known in the art (e.g. see *J. Med. Chem.*, 1992, 35, 248 where P¹, P² and P³ are each acetyl).

Alternatively, the compounds of the formula (I) may be prepared according to Scheme 3, wherein X is a leaving group, preferably chloro, by sulphonylation of
20 a compound of formula (XVIII) with a compound of the formula (VII).

25

30

Scheme 3



- 5 In a typical procedure, the compound of formula (XVIII) is dissolved in a suitable solvent such as 1,4-dioxan or tetrahydrofuran (with heating if necessary) and treated, typically at room temperature and under an atmosphere of nitrogen, with a sulphonylating agent of the formula (VII), optionally in the presence of an acid acceptor (e.g. triethylamine). Compounds
- 10 of the formula (XVIII) may be prepared by the reduction of a compound of the formula (XIX). The reduction may be carried out with any suitable hydride reducing agent or by hydrogenation. In a typical procedure, a solution of the compound of formula (XIX) in a suitable solvent such as ethanol is saturated with ammonia gas, treated with an appropriate hydrogenation catalyst such as
- 15 5% w/w palladium on charcoal and pressurised with hydrogen, preferably to 1034 kPa (150 psi). Compounds of the formula (XIX) may be prepared by the

deprotection of a compound of the formula (XV) according to methods known in the art [see for instance 'Protecting Groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. The protecting groups may be removed together, individually or in any
5 combination thereof. In a typical example, where P^1 , P^2 and P^3 are each acetyl, a solution of the compound of the formula (XV) in a suitable solvent such as ethanol is treated with a base such as ammonia at room temperature. In certain cases, deprotection and reduction of a compound of the formula (XV) to furnish a compound of the formula (XVIII) may be conveniently carried out together
10 under reducing conditions. In a typical example, the compound of the formula (XV) is dissolved in a suitable solvent such as ethanol and the solution is saturated with ammonia prior to treatment with an appropriate hydrogenation catalyst such as palladium on carbon and pressurisation with hydrogen to 1034 kPa (150 psi).

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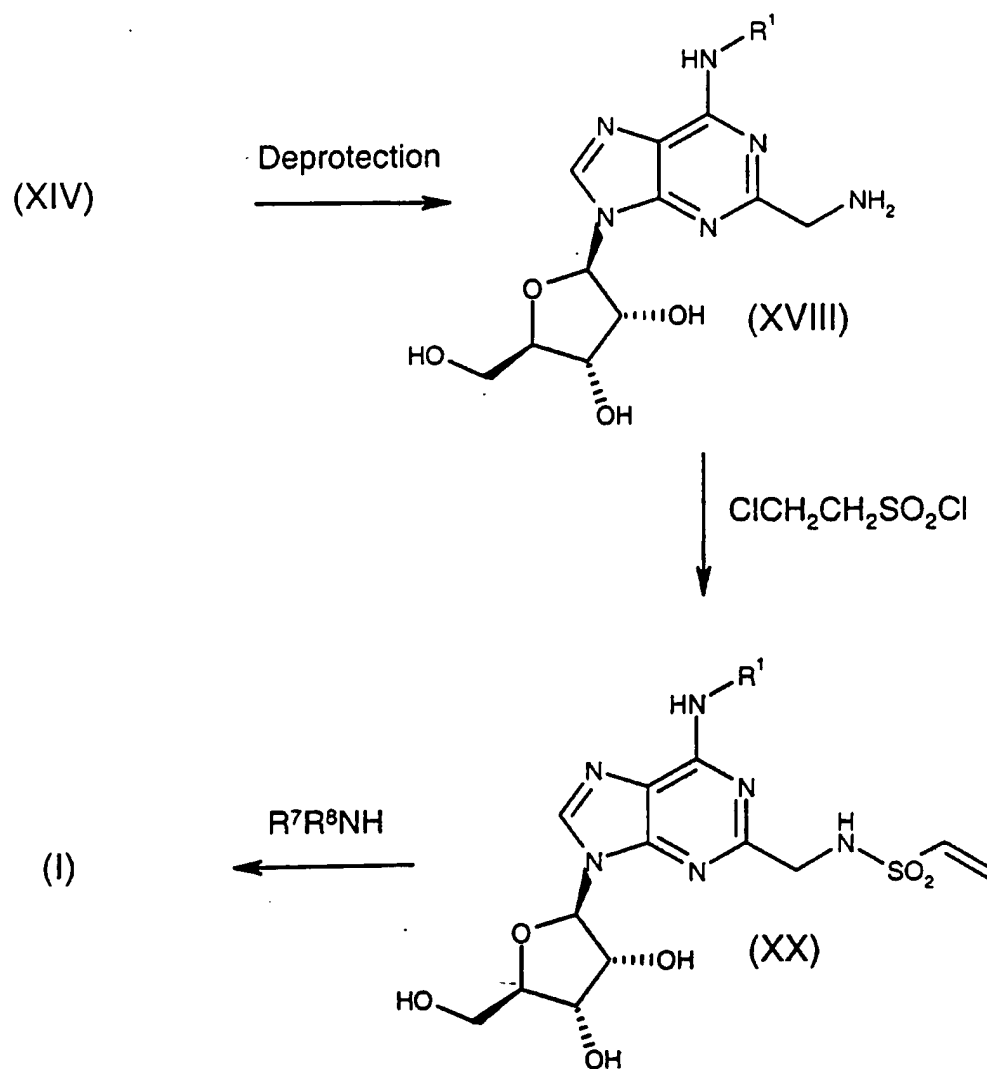
Compounds of the formula (I) in which A is $-\text{CH}_2\text{CH}_2-$ and R^2 is NR^7R^8 may also be prepared by the route shown in Scheme 4.

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Scheme 4



5

In Scheme 4, compounds of the formula (I) in which A is $-\text{CH}_2\text{CH}_2-$ and R^2 is $-\text{NR}^7\text{R}^8$ may be prepared by the reaction of a compound of the formula (XX) with a compound of the formula

10

 $\text{R}^7\text{R}^8\text{NH}$ (XXII).

In a typical procedure, the compound of the formula (XX) and the compound of the formula (XXII) are mixed, optionally in the presence of a suitable solvent. Preferably, the reaction mixture is heated, most preferably at the reflux temperature of the compound of the formula (XXII). Compounds of the formula (XXII) are either commercially available or easily prepared using standard procedures well known to those skilled in the art (e.g. the reductive condensation of an amine with a ketone or an aldehyde). Compounds of the formula (XX) may be prepared by the condensation of a compound of the formula (XVIII) with 2-chloroethanesulphonyl chloride. In a typical procedure, a solution of the compound of the formula (XVIII) and a base, preferably a tertiary amine base such as triethylamine, in a suitable solvent, such as dichloromethane, is treated with 2-chloroethanesulphonyl chloride. Compounds of the formula (XVIII) may be prepared by the deprotection of a compound of the formula (XIV) in which protecting groups P^1 , P^2 and P^3 are as defined above. The protecting groups may be removed together, or singly in any combination thereof. Suitable conditions for the deprotection are well known in the art [see for instance 'Protecting Groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical procedure, where P^1 , P^2 and P^3 are each acetyl, the protecting groups may be removed by treating a solution of the compound of formula (XIV) in a suitable solvent, such as a mixture of water and methanol, with a base such as sodium carbonate, typically at room temperature.

Compounds of the formula (I) may also be interconverted using conventional functional group interconversion techniques.

All of the reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions as well as procedures for isolating the desired products will be well-known to persons skilled in the art with reference to literature precedents and the Examples and Preparations sections below.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the
5 solvent.

The anti-inflammatory properties of the compounds of the formula (I) are demonstrated by their ability to inhibit neutrophil function which indicates A2a receptor agonist activity. This is evaluated by determining the compound profile
10 in an assay where superoxide production is measured from neutrophils activated by fMLP. Neutrophils were isolated from human peripheral blood using dextran sedimentation followed by centrifugation through Ficoll-Hypaque solution. Any contaminating erythrocytes in the granulocyte pellet were removed by lysis with ice-cold distilled water. Superoxide production from the
15 neutrophils was induced by fMLP in the presence of a priming concentration of cytochalasin B. Adenosine deaminase was included in the assay to remove any endogenously produced adenosine that might suppress superoxide production. The effect of the compound on the fMLP-induced response was monitored colorimetrically from the reduction of cytochrome C within the assay buffer.
20 The potency of the compounds was assessed by the concentration giving 50% inhibition (IC_{50}) compared to the control response to fMLP.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent
25 or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the formula (I) can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions
30 or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, sustained-, pulsed- or controlled-release applications.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and
5 granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

10 Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or a high molecular weight polyethylene glycol. For aqueous suspensions and/or elixirs, the compounds of the formula (I) may be combined with various sweetening or flavouring agents, colouring matter or
15 dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol or glycerin, and combinations thereof.

The compounds of the formula (I) can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally,
20 intraventricularly, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. They are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a
25 pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level
30 of the compounds of the formula (I) will usually be from 0.01 to 100 mg/kg, preferably from 0.1 to 100 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the formula (I) may contain from 5 to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

10 The compounds of formula (I) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 15 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol 20 and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) and a suitable powder base such as lactose or starch. 25

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 20 to 4000 μg of a compound of the formula (I) for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 20 μg to 20mg which may be administered in a single 30 dose or, more usually, in divided doses throughout the day.

Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. The compounds of the formula (I) may also be transdermally administered, for example, by the use of
5 a skin patch.

For application topically to the skin, the compounds of the formula (I) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following:
10 mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60,
15 cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the formula (I) may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may
20 modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-
25 cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

30

Thus the invention provides:-

- (i) a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a process for the preparation of a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;
- 5 (iii) a pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;
- (iv) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;
- 10 (v) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament to treat a disease for which a A2a receptor agonist is indicated;
- (vi) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of
15 an anti-inflammatory agent;
- (vii) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a respiratory disease;
- 20 (viii) use as in (vii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;
- (ix) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a
25 medicament for the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, allergic dermatitis, eczema, ulcerative colitis,
30 Crohns disease, inflammatory bowel disease, *Helicobacter pylori*-gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-

induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing;

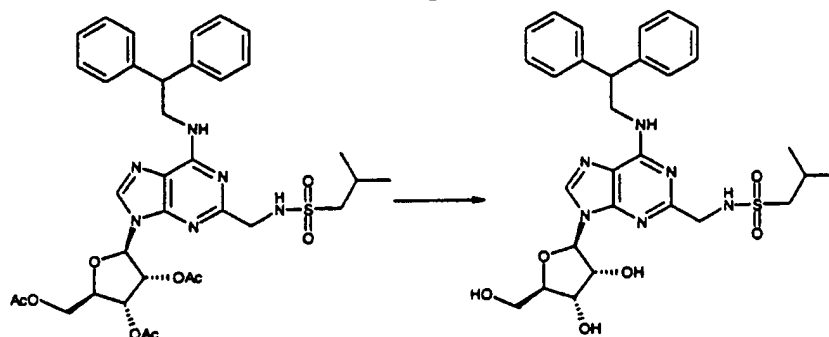
- 5 (x) a method of treatment of a mammal, including a human being, to treat a disease for which a A2a receptor agonist is indicated including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;
- 10 (xi) a method of treatment of a mammal, including a human being, to treat an inflammatory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;
- 15 (xii) a method of treatment of a mammal, including a human being, to treat a respiratory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;
- (xiii) a method as in (xii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;
- 20 (xiv) a method of treatment of a mammal, including a human being, to treat septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori*-gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing, including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof; and
- 25 30 (xv) certain novel intermediates disclosed herein.

The following Examples illustrate the preparation of the compounds of the formula (I):-

¹H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: *e.g.* s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The mass spectra (m/z) were recorded in the thermospray ionisation mode. The following abbreviations have been used for common solvents: CDCl₃, deuteriochloroform; DMSO, dimethylsulphoxide. The abbreviation psi means pounds per square inch. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F₂₅₄ plates, R_f is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate. The abbreviation Ac has been used in place of acetyl and TBDMS means tert-butyltrimethylsilyl.

EXAMPLE 1:

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl)-2-methyl-1-propanesulfonamide



A solution of (2*R*,3*R*,4*R*,5*R*)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-(6-[(2,2-diphenylethyl)amino]-2-[[[(isobutylsulfonyl)amino]methyl]-9*H*-purin-9-yl)tetrahydro-3-furanyl acetate (188mg, 0.26mmol) (Preparation 9) and sodium carbonate (140mg, 1.32mmol) in a mixture of water (2ml) and methanol (10ml) was stirred at room temperature for 6 hours. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and brine. The organic phase was separated and the solvent removed under reduced pressure. The residue was then purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol : 0.88 ammonia (95 : 5 : 0.5 by volume) gradually changing to dichloromethane : methanol : 0.88 ammonia (90 : 10 : 1 by volume) to afford the title compound (77mg).

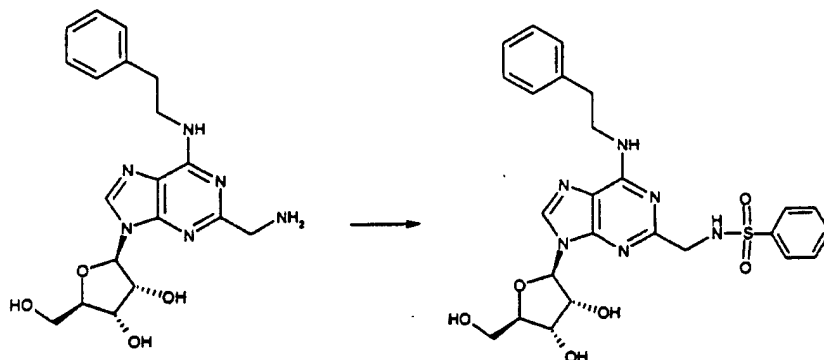
MS: 597 (MH⁺); 619 (MNa⁺).

¹H-NMR (CDCl₃) δ : 7.60 (1H, br s), 7.20-7.38 (10H, m), 6.02 (1H, br s), 5.91 (1H, br d), 5.81 (1H, t), 5.70 (1H, d), 4.83 (1H, br s), 4.50 (1H, d), 4.07-4.40 (7H, m), 3.90 (1H, d), 3.75 (1H, t), 3.32 (1H, s), 2.95 (2H, d), 2.26 (1H, m), 4.06 (6H, d).

Analysis : Found C, 57.54; H, 6.10; N, 13.76%; C₂₉H₃₆N₆O₆S. 0.5H₂O requires C, 57.52; H, 6.11; N, 13.88%.

EXAMPLE 2:

***N*-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-(phenethylamino)-9*H*-purin-2-yl]methyl}benzenesulfonamide**



5

A solution of benzenesulphonyl chloride (0.067g, 0.38mmol) in dry tetrahydrofuran (2ml) was added over 10 minutes to a stirred solution of (2*R*,3*R*,4*S*,5*R*)-2-[2-(aminomethyl)-6-(phenethylamino)-9*H*-purin-9-yl]-5-(hydroxymethyl)tetrahydro-3,4-furandiol (0.19g, 0.48mmol) (Preparation 12) and triethylamine (0.14g, 1.39mmol) in dry tetrahydrofuran (10ml) at 0°C under an atmosphere of nitrogen. The mixture was stirred at 0°C for 15 minutes. The solvent was then removed under reduced pressure and the residue azeotroped with dichloromethane (x3). The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (92 : 8 : 0.4 by volume), to give the product which was triturated with diethyl ether, filtered and dried to afford the title compound as a solid (200mg).

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MS: 540 (MH⁺).

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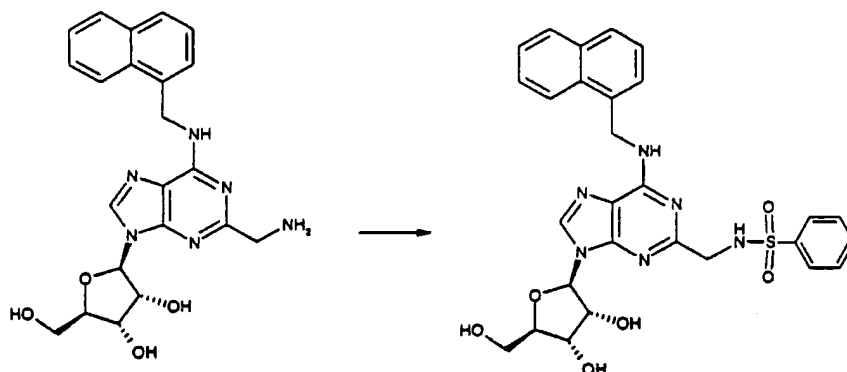
¹H-NMR (CDCl₃) δ : 7.82 (2H, d), 7.63 (1H, s), 7.16-7.45 (8H, m), 6.02-6.22 (2H, m), 5.96 (1H, br s), 5.70 (1H, d), 4.82 (1H, m), 4.47 (1H, d), 4.02-4.34 (4H, m), 3.62-3.98 (4H, m), 3.37 (1H, s), 2.92 (2H, t).

25

EXAMPLE 3:

N-[(9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(1-naphthylmethyl)amino]-9*H*-purin-2-yl)methyl]benzenesulfonamide

5



A suspension of (2*R*,3*R*,4*S*,5*R*)-2-[2-(aminomethyl)-6-[(1-naphthylmethyl)amino]-9*H*-purin-9-yl]-5-(hydroxymethyl)tetrahydro-3,4-furandiol (0.16g, 0.37mmol) (Preparation 15) in dioxan (28ml) was heated gently until a solution was achieved. The solution was cooled to room temperature and treated with triethylamine (0.12g, 1.19mmol) followed by addition of a solution of benzenesulphonyl chloride (0.060g, 0.34mmol) in dioxan (2ml) over 10 minutes. The mixture was then stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure and the residue azeotroped with dichloromethane. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (92 : 8 : 0.4 by volume) to afford the title compound as a white solid (150mg).

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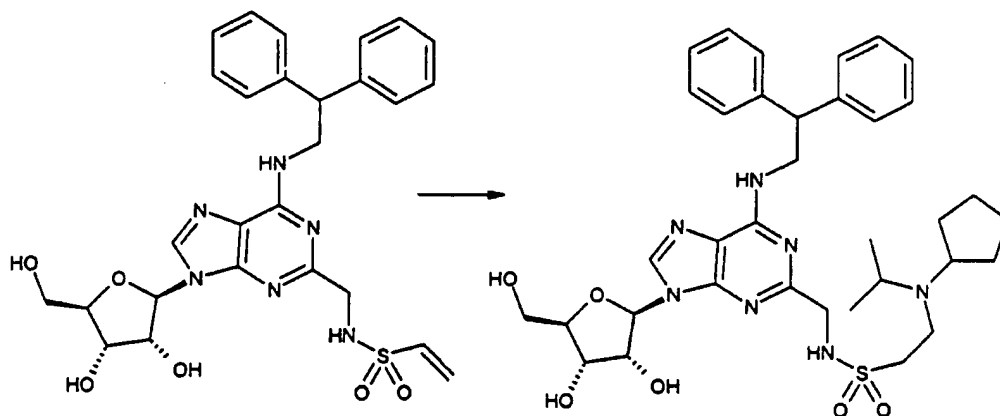
MS: 577 (MH⁺).

¹H-NMR (DMSO-*d*₆) δ : 8.15-8.40 (3H, m), 7.20-7.98 (12H, m), 5.85 (1H, d), 5.38 (1H, d), 5.00-5.36 (4H, m), 4.52 (1H, q), 4.13 (1H, m), 4.00 (2H, s), 3.92 (1H, d), 3.42-3.72 (2H, m).

25

EXAMPLE 4:

2-[Cyclopentyl(isopropyl)amino]-*N*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl)ethanesulfonamide



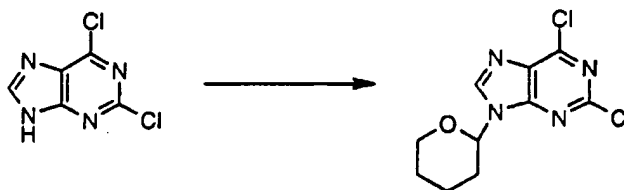
N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl)ethanesulfonamide (60 mg, 0.11 mmol) (Preparation 16) was dissolved in *N*-isopropylcyclopentanamine (2ml) (Preparation 17) and the reaction mixture was heated under reflux for two hours. The excess reagent was removed under reduced pressure and the residue was partitioned between dichloromethane (50ml) and water (30ml). The organic layer was evaporated and dried (anhydrous magnesium sulphate) and the residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (92:7:1 by volume) to give the title compound (13mg) as an oil.

MS: 695 (MH⁺).

¹H-NMR (CD₃OD) δ : (1H, s), 7.35-7.20 (10H, m), 6.00-5.95 (1H, m), 4.70-4.65 (1H, m), 4.55-4.50 (1H, m), 4.35-4.25 (6H, m), 4.15 (1H, s), 3.90-3.85 (1H, m), 3.75-3.70 (1H, m), 3.15-3.10 (2H, m), 3.00-2.90 (2H, m), 2.90-2.80 (2H, m), 1.70-1.60 (2H, m), 1.60-1.50 (2H, m), 1.50-1.40 (2H, m), 1.35-1.15 (2H, m), 0.9-0.85(6H, m).

The following Preparations describe the preparation of certain intermediates used in the preceding Examples.

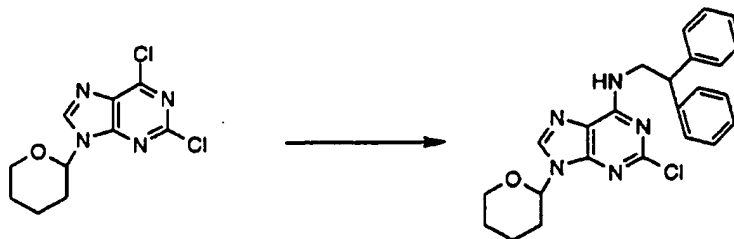
5 PREPARATION 1: 2,6-Dichloro-9-tetrahydro-2H-pyran-2-yl-9H-purine



2,6-Dichloro-9H-purine (20g, 0.11mol) and 4-toluenesulphonic acid monohydrate (0.2g) were dissolved in ethyl acetate (300ml), the mixture was heated to 50°C and a solution of 2,3-dihydropyran (12.6ml, 0.14mol) in ethyl acetate (50ml) was added slowly over 30min. The reaction mixture was then cooled to room temperature, water (100ml) was added and the pH of the solution was adjusted to 7 with a saturated aqueous solution of sodium hydrogen carbonate. The layers were separated and the organic layer was washed sequentially with water and brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was azeotroped from pentane (x2) to afford the title compound as a slightly impure white solid (30.9g).

¹H-NMR (CDCl₃) δ : 8.30 (1H, s), 5.75 (1H, dd), 4.25-4.15 (1H, m), 3.85-3.70 (1H, m), 2.20-1.60 (6H, m).

PREPARATION 2: 2-Chloro-N-(2,2-diphenylethyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine

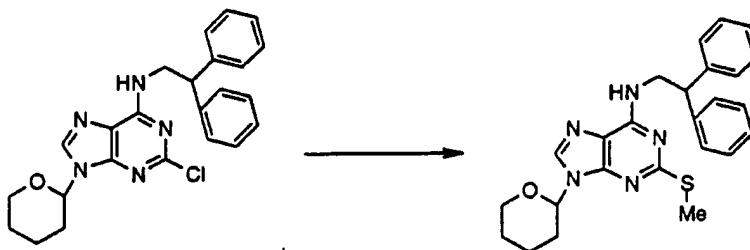


A solution of 2,6-dichloro-9-tetrahydro-2H-pyran-2-yl-9H-purine (Preparation 1) (30.9g, 0.11mol) in isopropyl alcohol (600ml) was treated with *N*-ethyl-*N*-isopropyl-2-propanamine (47.5ml, 0.27mol) and 2,2-diphenylethylamine (24.8g, 0.13mol) and the resulting mixture was heated at reflux for 3 hours. The solvent was removed under reduced pressure and the residue was azeotroped from ethyl acetate. The residue was purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate : hexane (40 : 60 by volume) gradually changing to ethyl acetate : hexane (60 : 40 by volume) to afford the title compound as a foam (49.7g).

10

¹H-NMR (CDCl₃) δ : 7.95-7.75 (1H, br s), 7.35-7.15 (10H, m), 5.80-5.70 (1H, br s), 5.65 (1H, d), 4.35 (1H, m), 4.30-4.18 (1H, br s), 4.10 (1H, d), 3.70 (1H, t), 2.05-1.95 (2H, m), 1.95-1.80 (1H, m), 1.80-1.55 (3H, m).

15 **PREPARATION 3: *N*-(2,2-Diphenylethyl)-2-(methylsulfanyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine**



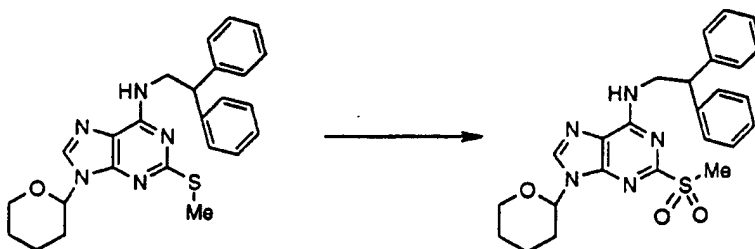
A solution of 2-chloro-*N*-(2,2-diphenylethyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine (Preparation 2) (49.7g, 0.11mol) in dry *N,N*-dimethylformamide (200ml) was treated with sodium thiomethoxide (10g, 0.14mol) and the resulting mixture heated under an atmosphere of nitrogen at 100°C for 90 minutes. The mixture was stirred at room temperature for 72 hours and then reheated to 100°C for a further 2 hours. The reaction mixture was cooled and diluted with water (1000ml). A suspension was formed which was extracted into diethyl ether (x2). The combined organic layers were washed sequentially with water and brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was azeotroped from diethyl ether and

25

then pentane to afford the title compound as a foam (48.9g).

¹H-NMR (CDCl₃) δ : 7.80 (1H, s), 7.20-7.10 (10H, m), 5.70-5.55 (2H, d), 4.40-4.20 (3H, m), 4.20-4.05 (1H, m), 3.80-3.65 (1H, m), 2.60 (3H, s), 2.15-1.90 (3H, m), 1.90-1.60 (3H, m).

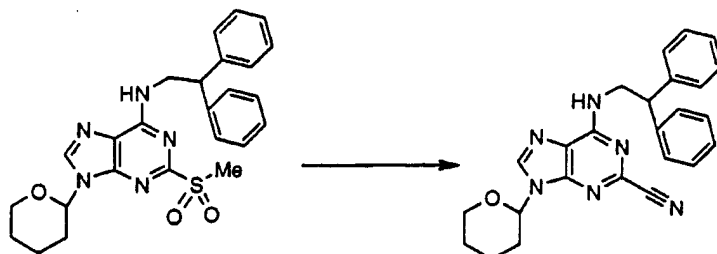
PREPARATION 4: *N*-(2,2-Diphenylethyl)-2-(methylsulfonyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine



- 10 A solution of Oxone (trade mark) (potassium peroxymonosulphate) (44g, 71.7mmol) in water (200ml) was added dropwise over 2 hours to a solution of *N*-(2,2-diphenylethyl)-2-(methylsulfonyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine (Preparation 3) (25g, 56.2mmol) and sodium hydrogen carbonate (20g, 238mmol) in acetone (1000ml) and water (250ml). The resulting mixture was
- 15 stirred at room temperature for 24 hours, filtered and the residue washed with acetone. The acetone was removed from the filtrate under reduced pressure and the resulting aqueous residue extracted with ethyl acetate and then dichloromethane. The combined organic layers were washed with brine, dried with anhydrous magnesium sulphate, filtered and evaporated under reduced
- 20 pressure. The residue was triturated with diethyl ether, filtered, washed with diethyl ether and pentane and then dried to afford the title compound as a white solid (20.32g).

¹H-NMR (CDCl₃) δ : 8.00 (1H, s), 7.35-7.15 (10H, m), 6.05-5.95 (1H, br s), 5.75 (1H, d), 4.40-4.35 (1H, m), 4.35-4.20 (2H, br s), 4.15-4.05 (1H, m), 3.75 (1H, t), 3.30 (3H, s), 2.18-2.05 (1H, m), 2.05-1.98 (1H, m), 1.98-1.80 (1H, m), 1.80-1.60 (3H, m).

PREPARATION 5: 6-[(2,2-Diphenylethyl)amino]-9-tetrahydro-2H-pyran-2-yl-9H-purine-2-carbonitrile



5 A solution of *N*-(2,2-diphenylethyl)-2-(methylsulfonyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine (Preparation 4) (20.1g, 42.1mmol) in dry N,N-dimethylformamide (100ml) was treated with potassium cyanide (5.5g, 84.6mmol) and the mixture was heated at 120°C for 24 hours under a nitrogen atmosphere. The mixture was then cooled to room temperature, poured into
10 water (1000ml) and stirred for a further 1 hour. The resultant solid was slowly filtered and washed several times with water. The solid was then dissolved in dichloromethane and the resulting solution was washed with water, dried with anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was azeotroped from diethyl ether twice to afford the
15 title compound as an oil (17g).

¹H-NMR (CDCl₃) δ : 8.00 (1H, s), 7.40-7.20 (10H, m), 6.00-5.75 (1H, br s), 5.70 (1H, d), 4.40-4.20 (3H, m), 4.20-4.10 (1H, m), 3.80-3.70 (1H, m), 2.20-1.90 (3H, m), 1.90-1.60 (3H, m).

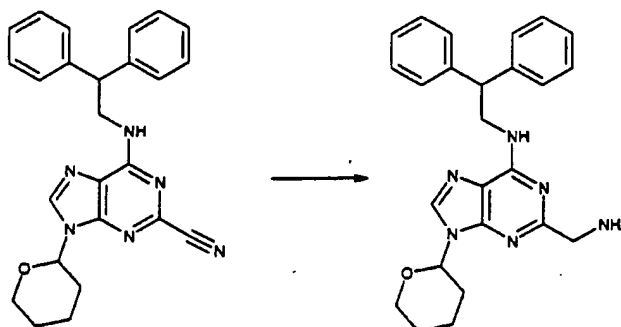
20

25

PREPARATION 6 :

***N*-[2-(Aminomethyl)-9-tetrahydro-2*H*-pyran-2-yl]-9*H*-purin-6-yl]-*N*-(2,2-diphenylethyl)amine**

5



A solution of 6-[(2,2-diphenylethyl)amino]-9-tetrahydro-2*H*-pyran-2-yl-9*H*-purine-2-carbonitrile (5.70g, 13.18mmol) (Preparation 5) in ethanol (200ml) saturated
10 with ammonia gas was treated with Pearlmann's catalyst (1.00g), pressurised to 60psi with hydrogen in a sealed vessel and stirred at room temperature for 30 hours. The mixture was filtered through a pad of Arbocel (trade mark) and the solvent was removed under reduced pressure. The residue was azeotroped from dichloromethane (x2) and then purified by column chromatography on
15 silica gel eluting with dichloromethane : methanol (95 : 5 by volume) gradually changing to dichloromethane : methanol : 0.88 ammonia (90 : 10 : 0.5 by volume) to afford the title compound (4.34g).

MS: 429 (MH⁺).

20

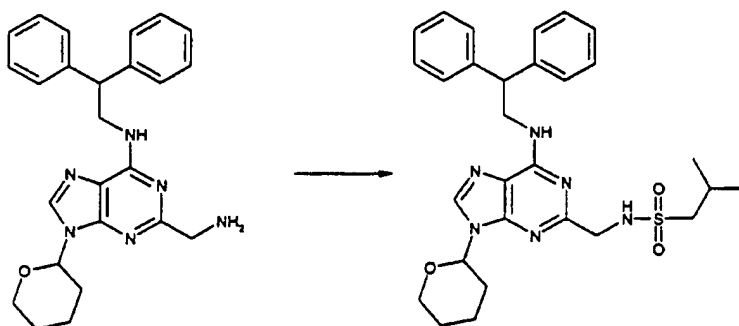
¹H-NMR (CDCl₃) δ : 7.84 (1H, s), 7.14-7.36 (10H, m), 5.70 (1H, d), 5.50-5.70 (1H, br s), 4.20-4.42 (3H, m), 4.14 (1H, d), 3.95 (2H, s), 3.78 (1H, t), 1.90-2.20 (5H, m), 1.50-1.88 (3H, m).

25

PREPARATION 7 :

N-((6-[(2,2-Diphenylethyl)amino]-9-tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl)methyl)-2-methyl-1-propanesulfonamide

5



A solution of *N*-[2-(aminomethyl)-9-tetrahydro-2*H*-pyran-2-yl]-*N*-(2,2-diphenylethyl)amine (3.70g, 8.63mmol) (Preparation 6) and triethylamine (2.20g, 21.78mmol) in dry dichloromethane (20ml) was treated with 2-methyl-1-propanesulfonyl chloride (1.48g, 9.46mmol) and the mixture was stirred at room temperature for 18 hours. TLC indicated that some starting material still remained and so further 2-methyl-1-propanesulfonyl chloride (0.2g, 1.28mmol) was added and the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol (98 : 2 by volume) to afford the title compound as a foam (4.4g).

MS: 549 (MH⁺).

20

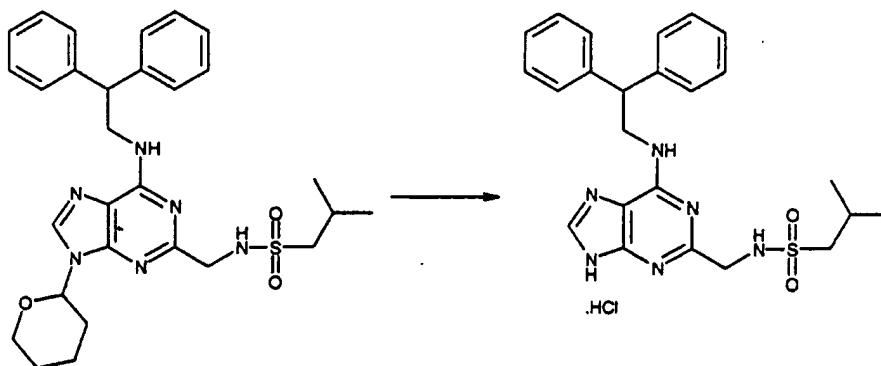
¹H-NMR (CDCl₃) δ : 7.86 (1H, s), 7.16-7.36 (10H, m), 5.74 (1H, br s), 5.64 (1H, d), 5.57 (1H, t), 4.18-4.46 (5H, m), 4.14 (1H, d), 3.77 (1H, t), 2.92 (2H, d), 2.28 (1H, m) 1.92-2.10 (3H, m), 1.58-1.88 (3H, m), 1.03 (6H, d).

25

PREPARATION 8 :

***N*-({6-[(2,2-Diphenylethyl)amino]-9*H*-purin-2-yl)methyl}-2-methyl-1-propanesulfonamide hydrochloride**

5



A solution of *N*-({6-[(2,2-diphenylethyl)amino]-9-tetrahydro-2*H*-pyran-2-yl-9*H*-purin-2-yl)methyl}-2-methyl-1-propanesulfonamide (4.30g, 7.84mmol)

10 (Preparation 7) in ethanol (100ml) was heated to 37°C and then treated with hydrochloric acid (2N, 15ml). The mixture was left to stand at room temperature for 18 hours, after which time a crystalline precipitate was filtered off, washed with ethanol (10ml) and dried to afford the title compound as a solid (3.0g).

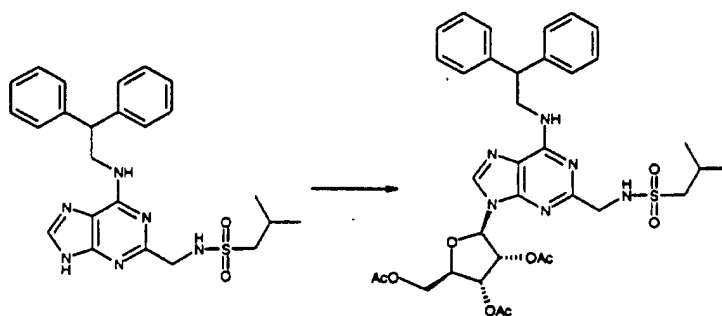
15 ¹H-NMR (DMSO-*d*₆) δ : 8.48 (1H, br s), 7.75 (1H, br s), 7.37 (4H, d), 7.27 (4H, dd), 7.16 (2H, dd), 4.56 (1H, t), 4.20-4.40 (4H, m), 2.95 (2H, d), 2.10 (1H, m), 0.95 (6H, d).

20

25

PREPARATION 9 :

(2*R*,3*R*,4*R*,5*R*)-4-(Acetyloxy)-2-[(acetyloxy)methyl]-5-(6-[(2,2-diphenylethyl)amino]-2-[[[(isobutylsulfonyl)amino]methyl]-9*H*-purin-9-yl)tetrahydro-3-furanyl acetate



A suspension of *N*-((6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl)-2-methyl-1-propanesulfonamide hydrochloride (Preparation 8) (0.21g, 0.42mmol) in 1,1,1-trichloroethane (10ml) was treated with *N*,*O*-bis(trimethylacetamide) (0.6ml, 2.45mmol) and the mixture was heated under reflux for 2 hours. The solvent was removed under reduced pressure and the residue was azeotroped with toluene (x2). The residue was dissolved in toluene (10ml) and treated with the β -D-ribofuranose-1,2,3,5-tetraacetate (0.16g, 0.50mmol) and trimethylsilyltriflate (0.1ml, 0.5mmol). The mixture was then heated at reflux for 4 hours. The mixture was diluted with ethyl acetate, washed sequentially with saturated aqueous sodium hydrogen carbonate solution and brine and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (98 : 2 by volume) gradually changing to dichloromethane : methanol (95 : 5 by volume) to afford the title compound as a 1:3 mixture of α - and β -anomers (188mg).

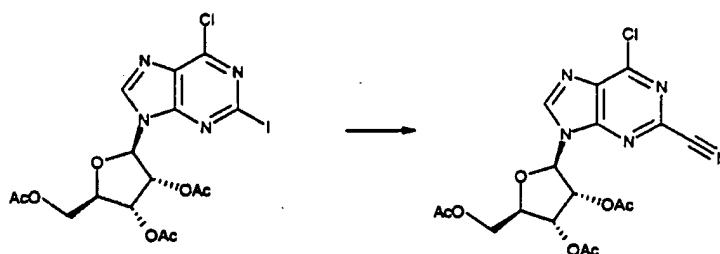
MS: 723 (MH^+); 745 (MNa^+).

¹H-NMR (CDCl₃) δ : 7.97 (0.25H, br s), 7.76 (0.75H, br s), 7.15-7.37 (10H, m), 7.25 (2.25H, m), 5.88 (1.75H, m), 5.73 (0.75H, m), 5.51 (0.25H, m), 4.34-4.63 (8H, m), 2.95 (2H, m), 2.28 (3H, s), 2.06-2.20 (4H, m), 2.00 (3H, s), 1.05 (6H, d).

5

PREPARATION 10 :

(2*R*,3*R*,4*R*,5*R*)-4-(Acetyloxy)-2-[(acetyloxy)methyl]-5-(6-chloro-2-cyano-9*H*-purin-9-yl)tetrahydro-3-furanyl acetate



10

A mixture of (2*R*,3*R*,4*R*,5*R*)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-(6-chloro-2-iodo-9*H*-purin-9-yl)tetrahydro-3-furanyl acetate (*J. Med. Chem.*, 1992, 35, 248) (0.5g, 0.93mmol) and copper (II) cyanide (0.11g, 1.23mmol) in N,N-dimethylformamide was heated at 115°C for 90 minutes. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with dichloromethane : ethyl acetate (4 : 1 by volume) to give a product which was then azeotroped sequentially with dichloromethane and diethyl ether to afford the title compound as a solid (0.22g).

20

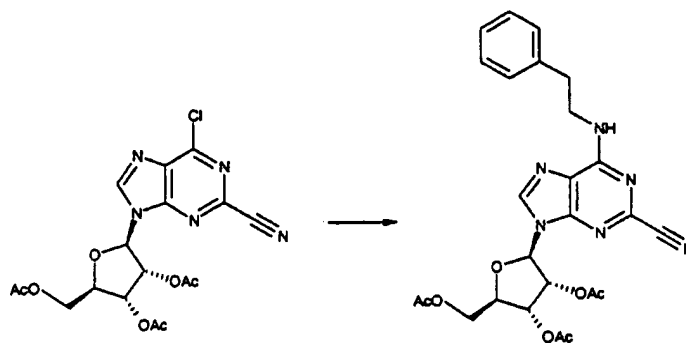
MS: 438 (MH⁺).

¹H-NMR (CDCl₃) δ : 8.50 (1H, s), 6.28 (1H, d), 5.78 (1H, t), 5.53 (1H, m), 4.52 (1H, m), 4.42 (2H, m), 2.20 (3H, s), 2.17 (3H, s), 2.10 (3H, s).

25

PREPARATION 11 :

(2*R*,3*R*,4*R*,5*R*)-4-(Acetyloxy)-2-[(acetyloxy)methyl]-5-[2-cyano-6-phenethylamino)-9*H*-purin-9-yl]tetrahydro-3-furanyl acetate



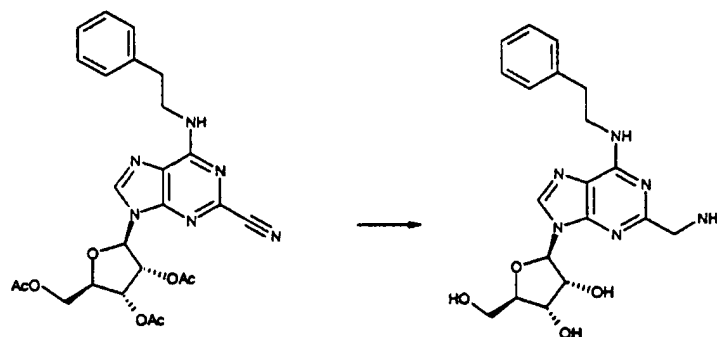
A solution of (2*R*,3*R*,4*R*,5*R*)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-(6-chloro-2-cyano-9*H*-purin-9-yl)tetrahydro-3-furanyl acetate (1.96g, 4.48mmol) (Preparation 10) and triethylamine (1.8g, 17.8mmol) in acetonitrile (20ml) was treated with phenethylamine (0.60g, 4.96mmol) and the mixture was stirred at room temperature under a nitrogen atmosphere for 2 hours. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (75ml) and water (20ml). The organic phase was separated and the solvent was removed under reduced pressure. The foam was purified by column chromatography on silica gel eluting with dichloromethane : ethyl acetate (4 : 1 by volume) to give a product which was then azeotroped with diethyl ether to afford the title compound as a foam (2.05g).

MS: 523 (MH⁺).

¹H-NMR (CDCl₃) δ : 8.00 (1H, s), 7.17-7.35 (5H, m), 6.16 (1H, d), 6.03 (1H, br s), 5.77 (1H, m), 5.57 (1H, m), 4.34-4.47 (3H, m), 3.80-4.00 (2H, br s), 2.98 (2H, m), 2.16 (3H, s), 2.14 (3H, s), 2.08 (3H, s).

PREPARATION 12 :

(2*R*,3*R*,4*S*,5*R*)-2-[2-(Aminomethyl)-6-(phenethylamino)-9*H*-purin-9-yl]-5-(hydroxymethyl)tetrahydro-3,4-furandiol



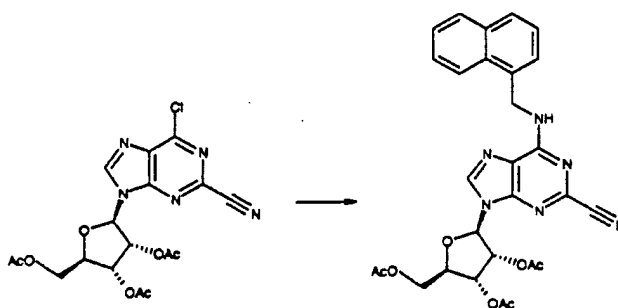
A solution of (2*R*,3*R*,4*R*,5*R*)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-[2-cyano-6-
10 (phenethylamino)-9*H*-purin-9-yl]tetrahydro-3-furanyl acetate (1.0g, 1.91mmol)
(Preparation 11) in ethanol (40ml) saturated with ammonia gas was treated with
5% w/w palladium on charcoal (0.50g), pressurised to 1034 kPa (150psi) with
hydrogen in a sealed vessel and stirred at room temperature for 18 hours. TLC
analysis showed that some starting material still remained and therefore further
15 5% w/w palladium on charcoal (0.25g) and ethanol (20ml) saturated with
ammonia were added and the mixture was again pressurised to 1034 kPa
(150psi) with hydrogen in a sealed vessel and stirred at room temperature for
18 hours. The mixture was filtered through a pad of Arbocel (trade mark) and
the filtrate was evaporated under reduced pressure. The residue was
20 azeotroped from dichloromethane, then purified by column chromatography on
silica gel eluting with dichloromethane : methanol : 0.88 ammonia (90 : 10 : 0.5
by volume) to afford the title compound as a white solid (340mg).

MS: 401 (MH⁺).

¹H-NMR (DMSO-d₆) δ : 8.28 (1H, br s), 7.91 (1H, br s), 7.14-7.33 (5H, m), 5.90 (1H, d), 5.38 (1H, br s), 5.17 (1H, br s), 4.61 (1H, br s), 4.13 (1H, br s), 3.95 (1H, s), 3.73 (5H, m), 3.66 (1H, dd), 3.52 (1H, dd), 2.90 (2H, t).

5 PREPARATION 13 :

(2*R*,3*R*,4*R*,5*R*)-4-(Acetyloxy)-2-[(acetyloxy)methyl]-5-{2-cyano-6-[(1-naphthylmethyl)amino]-9*H*-purin-9-yl}tetrahydro-3-furanyl acetate



10

A solution of (2*R*,3*R*,4*R*,5*R*)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-(6-chloro-2-cyano-9*H*-purin-9-yl)tetrahydro-3-furanyl acetate (3.0g, 6.86mmol) (Preparation 10), 1-naphthalenemethylamine (1.2g, 7.63mmol), and triethylamine (2.8g, 27.72mmol) in acetonitrile (30ml) was left to stand at room temperature for 2 hours during which time a fine precipitate slowly formed. The solvent was removed under reduced pressure and the residue partitioned between dichloromethane (150ml) and water (50ml). The organic phase was separated and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : ethyl acetate (4 : 1 by volume) to give a product which was azeotroped with dichloromethane to afford the title compound as a foam (3.6g).

20

MS: 559 (MH⁺).

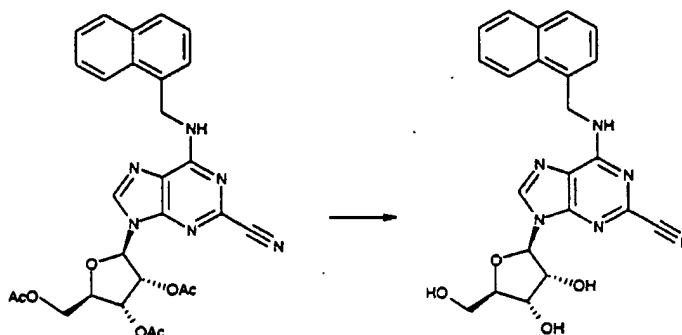
¹H-NMR (CDCl₃) δ : 7.78-8.10 (4H, m), 7.38-7.62 (4H, m), 6.22 (1H, br s), 6.16 (1H, d), 5.78 (1H, t), 5.56 (1H, m), 5.24 (2H, br s), 4.36-4.48 (3H, m), 2.18 (3H, s), 2.15 (3H, s), 2.10 (3H, s).

25

PREPARATION 14 :

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(1-naphthylmethyl)amino]-9*H*-purine-2-carbonitrile

5



A solution of (2*R*,3*R*,4*R*,5*R*)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-(2-cyano-6-[(1-naphthylmethyl)amino]-9*H*-purin-9-yl)tetrahydro-3-furanyl acetate (3.5g, 6.27mmol) (Preparation 13) in ethanol (120ml) was saturated with ammonia gas and stirred at room temperature for 4 days. The solvent was removed under reduced pressure and the residue was triturated with water (100mls), filtered and dried to afford the title compound as a solid (2.4g).

15

MS: 433 (MH⁺).

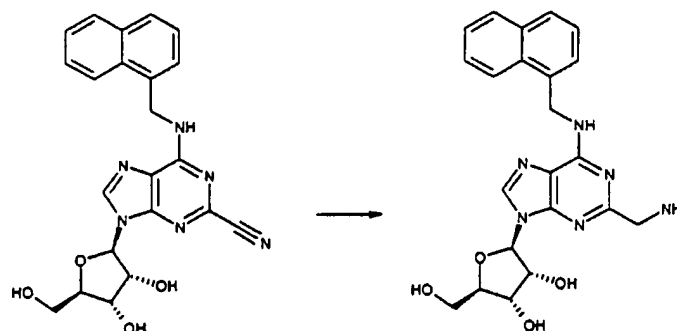
¹H-NMR (DMSO-d₆) δ : 9.12 (1H, br s), 8.67 (1H, s), 8.24 (1H, d), 7.94 (1H, d), 7.82 (1H, m), 7.34-7.63 (4H, m), 5.91 (1H, d), 5.50 (1H, br s), 4.90-5.30 (4H, m), 4.53 (1H, m), 4.14 (1H, br s), 3.95 (1H, m), 3.60 (2H, m).

20

25

PREPARATION 15 :

(2*R*,3*R*,4*S*,5*R*)-2-{2-(Aminomethyl)-6-[(1-naphthylmethyl)amino]-9*H*-purin-9-yl}-5-(hydroxymethyl)tetrahydro-3,4-furandiol



5

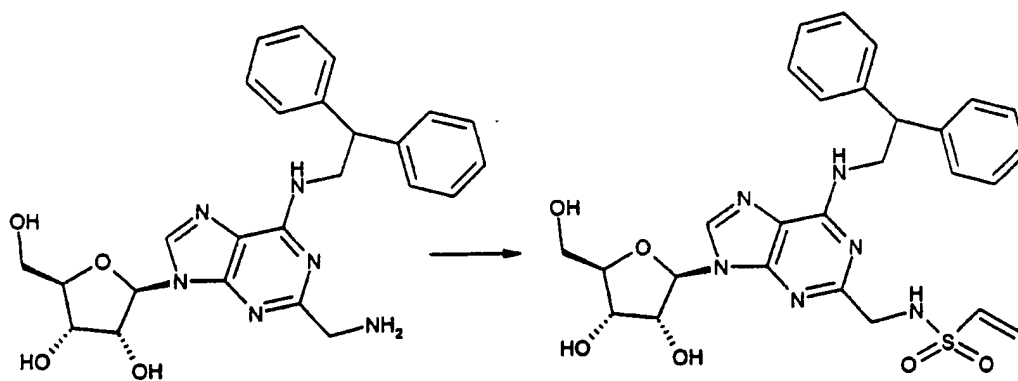
A solution of 9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(1-naphthylmethyl)amino]-9*H*-purine-2-carbonitrile (0.75g, 1.74mmol) (Preparation 14) in ethanol (30ml) was saturated with ammonia gas, treated
10 with 5% w/w palladium on charcoal (0.50g), pressurised to 1034 kPa (150psi) with hydrogen in a sealed vessel and stirred at room temperature for 42 hours. TLC analysis indicated that some starting material still remained and therefore further 5% w/w palladium on charcoal (0.30g) and ethanol (10ml) saturated with ammonia gas were added. The mixture was re-pressurised to 1034 kPa
15 (150psi) with hydrogen in a sealed vessel and stirred at room temperature for 24 hours. The mixture was filtered through a pad of Arbocel (trade mark) and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol : 0.88 ammonia (90 : 10 : 0.5 by volume) gradually
20 changing to dichloromethane : methanol : 0.88 ammonia (85 : 15 : 0.75 by volume) to afford the title compound (0.18g).

MS: 437 (MH⁺).

¹H-NMR (DMSO-d₆) δ : 8.42 (1H, br s), 8.28 (2H, br s), 7.93 (1H, d), 7.80 (1H, d), 7.36-7.60 (4H, m), 5.88 (1H, d), 5.38 (1H, br s), 5.18 (3H, br s), 4.60 (1H, br m), 4.13 (1H, br s), 3.95 (1H, m), 3.71 (2H, s), 3.63 (1H, dd), 3.57 (1H, dd).

5 PREPARATION 16:

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl)ethanesulfonamide



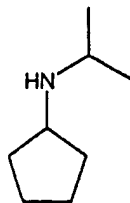
10

2-Chloroethanesulfonyl chloride (0.06ml, 0.58mmol) was added to a solution of (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(hydroxymethyl)tetrahydro-3,4-furandiol (250mg, 0.52mmol) (Preparation 19) and triethylamine (0.15ml, 1.1mmol) in dichloromethane (5ml). The reaction mixture was stirred for two hours at room temperature then diluted with more dichloromethane (50ml) and washed with water (50ml). The organic layer was dried (anhydrous magnesium sulphate) and the solvent was evaporated to give a residue that was purified by column chromatography on silica gel eluting with methanol:dichloromethane (1:19 by volume) increasing in polarity to methanol:dichloromethane (1:9 by volume). The solvent was removed under reduced pressure to give the title compound (65mg) as an oil.

20

¹H-NMR (CD₃OD) δ : 8.15 (1H, s), 7.40-7.15 (10H, m), 6.70-6.55 (1H, m), 6.15-6.05 (1H, m), 6.00-5.95 (1H, m), 5.80-5.75 (1H, m), 4.75-4.70 (1H, m), 4.55-4.50 (1H, m), 4.35-4.15 (6H, m), 3.95-3.85 (1H, m), 3.80-3.70 (1H, m).

25

PREPARATION 17:***N*-Isopropylcyclopentanamine**

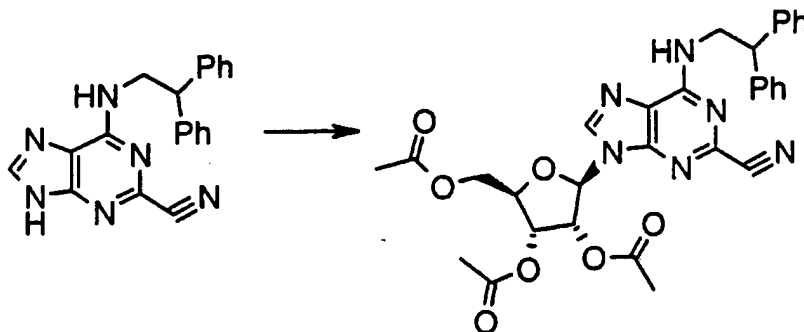
- 5 Sodium triacetoxyborohydride (33.76g, 0.16mol) was added to a solution of cyclopentylamine (15ml, 0.15mol) in acetone (500ml). The reaction mixture was stirred at room temperature for 24hr then the solvent was removed and the reaction mixture was partitioned between ethyl acetate (400ml) and 2M aqueous sodium hydroxide (150ml). The organic layer was separated, dried
- 10 (anhydrous magnesium sulphate) and evaporated under reduced pressure to give the title compound (12g) as a liquid.

¹H-NMR (CD₃OD) δ : 3.20-3.10 (1H, m), 2.95-2.80 (1H, m), 1.95-1.80 (2H, m), 1.75-1.45 (4H, m), 1.35-1.20 (2H, m), 1.10-1.00 (6H, m).

15

PREPARATION 18:

(2*R*,3*R*,4*R*,5*R*)-4-(Acetyloxy)-2-[(acetyloxy)methyl]-5-{2-cyano-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}tetrahydro-3-furanyl acetate



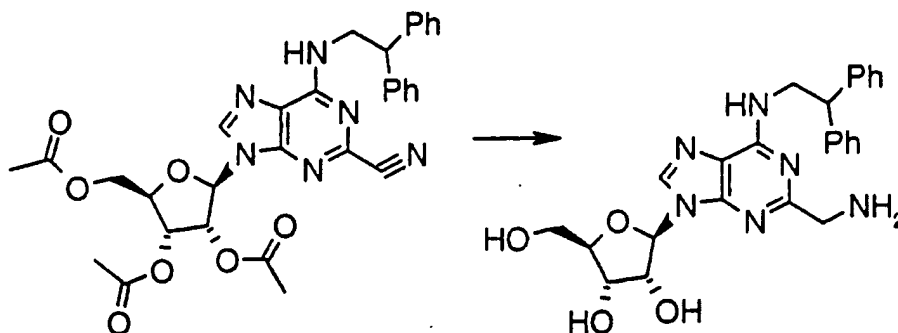
20

N,O-Bis(trimethylsilyl)acetamide (44ml, 0.18mol) was added to a suspension of 6-[(2,2-diphenylethyl)amino]-9*H*-purine-2-carbonitrile (10.0g, 0.03mol) (see WO-A-00/23457) in 1,1,1-trichloroethane (250ml). The suspension was heated to reflux. When all suspended solid had dissolved the reaction mixture was
5 allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was twice dissolved in toluene (50ml) and the solvent removed under reduced pressure. The residue was then dissolved in toluene (100ml) and (2*R*,3*R*,4*R*,5*S*)-4,5-bis(acetyloxy)-2-[(acetyloxy)methyl]tetrahydro-3-furanyl acetate (10.3g, 0.032mol) was added.
10 The solution was stirred at room temperature and trimethylsilyltrifluoromethanesulphonate (16ml, 0.088mol) was carefully added. The resulting solution was heated under reflux for 2 hours and then allowed to cool to room temperature. The reaction mixture was diluted by the addition of ethyl acetate (100ml) and then washed with saturated aqueous sodium
15 hydrogen carbonate (ten portions of 100ml) and saturated aqueous sodium chloride solution (100ml). The aqueous extracts were combined and washed with ethyl acetate (three portions of 100ml). The combined organic layers were dried (anhydrous magnesium sulphate) and the solvent was removed under reduced pressure to give a solid that was purified by column chromatography
20 on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (97 : 3 : 0.5 by volume gradually changing to 80 : 20 : 3 by volume) to give the title compound as a foam (8.5g).

¹H-NMR (CDCl₃) δ : 7.95 (1H, s), 7.35-7.20 (10H, m), 6.15-6.10 (1H, m), 5.95-
25 5.90 (1H, m), 5.80-5.75 (1H, m), 5.60-5.55 (1H, m), 4.45-4.35 (4H, m), 4.35-4.25 (2H, m), 2.15 (3H, s), 2.10 (3H, s), 2.05 (3H, s).

PREPARATION 19:

(2*R*,3*R*,4*S*,5*R*)-2-{2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(hydroxymethyl)tetrahydro-3,4-furandiol



5

10% w/w Palladium on carbon (200mg) was added to a solution of (2*R*,3*R*,4*R*,5*R*)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-{2-cyano-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}tetrahydro-3-furanyl acetate (Preparation 18) (1.9g, 3.2mmol) in ethanol saturated with ammonia (100ml). The reaction mixture was stirred under an atmosphere of hydrogen 414kPa (60psi) for 16 hours at room temperature. The solids were removed by filtration through Arbocel (Trade Mark) and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (90 : 10 : 1 by volume gradually changing to 80 : 20 : 2 by volume) to give the title compound as a solid (770mg).

15

MS: 477 (MH⁺).

20

¹H-NMR (CDCl₃) δ : 8.10 (1H, s), 7.35-7.20 (8H, m), 5.90-5.85 (1H, m), 4.75-4.70 (1H, m), 4.50-4.40 (1H, m), 4.30-4.20 (2H, m), 4.10 (1H, m), 3.90-3.80 (2H, m), 3.70-3.65 (1H, m).

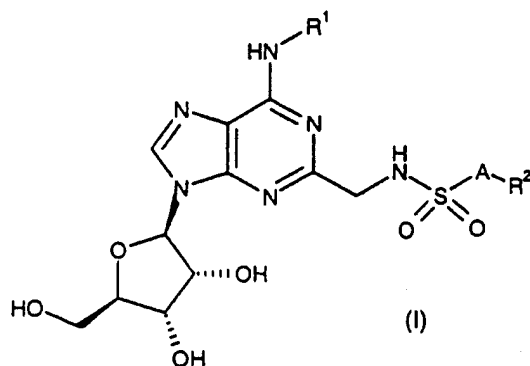
25

PHARMACOLOGICAL ACTIVITY

All the compounds of Examples 1-4 were tested for anti-inflammatory activity by their ability to inhibit neutrophil function (which indicates A2a receptor agonist activity) by the method described on page 20 and all had an IC₅₀ of less than 1 micromolar.

CLAIMS

1. A compound of the formula



5

or a pharmaceutically acceptable salt or solvate thereof, wherein

10 R^1 is hydrogen or C_1 - C_6 alkyl optionally substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl, said phenyl and naphthyl being optionally substituted by C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo or cyano;

A is a bond or C_1 - C_3 alkylene;

15

R^2 is (i) hydrogen, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, phenyl or naphthyl, said C_3 - C_7 cycloalkyl, phenyl or naphthyl being optionally substituted by C_1 - C_6 alkyl, phenyl, C_1 - C_6 alkoxy-(C_1 - C_6)-alkyl, R^3R^3N -(C_1 - C_6)-alkyl, fluoro-(C_1 - C_6)-alkyl, fluoro-(C_1 - C_6)-alkoxy, C_2 - C_5 alkanoyl, halo, $-OR^3$, cyano, $-COOR^3$, C_3 - C_7 cycloalkyl, $-S(O)_mR^4$, $-NR^3R^3$, $-SO_2NR^3R^3$, $-CONR^3R^3$, $-NR^3COR^4$ or $-NR^3SO_2R^4$, with the proviso that R^2 is not hydrogen when A is a bond,

20 or (ii) when A is C_2 - C_3 alkylene, $-NR^7R^8$, $-OR^3$, $-COOR^3$, $-OCOR^4$, $-SO_2R^4$, $-CN$, $-SO_2NR^3R^3$, $-NR^3COR^4$ or $-CONR^3R^3$,

or (iii) a C-linked, 4 to 11 membered, mono or bicyclic heterocycle having

25 either from 1 to 4 ring nitrogen atom(s) or 1 or 2 nitrogen and 1 oxygen or 1 sulphur ring atoms, optionally C-substituted by oxo, C_1 - C_6 alkoxy-(C_1 - C_6)-alkyl,

$R^3R^3N-(C_1-C_6)\text{-alkyl}$, fluoro-(C_1-C_6)-alkyl, fluoro-(C_1-C_6)-alkoxy, fluoro-(C_2-C_5)-
 alkanoyl, halo, cyano, $-OR^5$, R^6 , $-COR^5$, $-NR^5R^5$, $-COOR^5$, $-S(O)_mR^6$,
 $-SO_2NR^5R^5$, $-CONR^5R^5$, $-NR^5SO_2R^6$ or $-NR^5COR^6$ and optionally N-substituted
 by C_1-C_6 alkoxy-(C_1-C_6)-alkyl, $R^3R^3N-(C_2-C_6)\text{-alkyl}$, fluoro-(C_1-C_6)-alkyl, fluoro-
 5 (C_2-C_5)-alkanoyl, R^6 , $-COR^5$, $-COOR^5$, $-S(O)_mR^6$, $-SO_2NR^5R^5$ or $-CONR^5R^5$;

R^3 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl;
 10

R^4 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl;

15 R^5 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, naphthyl or het;

R^6 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, naphthyl or het;
 20

either, R^7 and R^8 , taken together with the nitrogen atom to which they are
 attached represent azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl,
 homopiperidinyl, homopiperazinyl or tetrahydroisoquinolinyl, each being
 25 optionally substituted on a ring carbon atom by C_1-C_6 alkyl, C_3-C_8 cycloalkyl,
 phenyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, $R^3R^3N-(C_1-C_6)\text{-alkyl}$, fluoro-(C_1-C_6)-alkyl, $-$
 $CONR^3R^3$, $-COOR^3$ or C_2-C_5 alkanoyl, and optionally substituted on a ring
 carbon atom not adjacent to a ring nitrogen atom by fluoro-(C_1-C_6)-alkoxy, halo,
 $-OR^3$, cyano, $-S(O)_mR^4$, $-NR^3R^3$, $-SO_2NR^3R^3$, $-NR^3COR^4$ or $-NR^3SO_2R^4$, and
 30 said piperazin-1-yl and homopiperazin-1-yl being optionally substituted on the
 ring nitrogen atom not attached to A by C_1-C_6 alkyl, phenyl, C_1-C_6 alkoxy-(C_2-

C₆)-alkyl, R³R³N-(C₂-C₆)-alkyl, fluoro-(C₁-C₆)-alkyl, C₂-C₅ alkanoyl, -COOR⁴, C₃-C₈ cycloalkyl, -SO₂R⁴, -SO₂NR³R³ or -CONR³R³,

or, R⁷ is H, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl or benzyl and R⁸ is H, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl, benzyl, fluoro-(C₁-C₆)-alkyl, -CONR³R³, -COOR⁴, C₂-C₅ alkanoyl or -SO₂NR³R³;

m is 0, 1 or 2; and

10 "het", used in the definitions of R⁵ and R⁶, means C-linked pyrrolyl, imidazolyl, triazolyl, thienyl, furyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, quinolinyl, isoquinolinyl, benzimidazolyl, quinazolinyl, phthalazinyl, benzoxazolyl or quinoxalinyl, each optionally substituted by C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano or halo.

15

2. A compound as claimed in claim 1 wherein

R¹ is hydrogen or C₁-C₆ alkyl optionally substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl, said phenyl and naphthyl
20 being optionally substituted by C₁-C₆ alkyl, C₁-C₆ alkoxy, halo or cyano;

A is a bond or C₁-C₃ alkylene;

R² is (i) hydrogen, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl or naphthyl, said C₃-C₇
25 cycloalkyl, phenyl or naphthyl being optionally substituted by C₁-C₆ alkyl, phenyl, C₁-C₆ alkoxy-(C₁-C₆)-alkyl, amino-(C₁-C₆)-alkyl, fluoro-(C₁-C₆)-alkyl, fluoro-(C₁-C₆)-alkoxy, C₂-C₅ alkanoyl, halo, -OR³, cyano, -COOR³, C₃-C₇ cycloalkyl, -S(O)_mR⁴, -NR³R³, -SO₂NR³R³, -CONR³R³, -NR³COR⁴ or -NR³SO₂R⁴, with the proviso that R² is not hydrogen when A is a bond,
30 or (ii) when A is C₂-C₃ alkylene, -NR³R³, -OR³, -COOR³, -OCOR⁴, -SO₂R⁴, -CN, -SO₂NR³R³, -NR³COR⁴ or -CONR³R³,

or (iii) a C-linked, 4 to 11 membered, mono or bicyclic heterocycle having either from 1 to 4 ring nitrogen atom(s) or 1 or 2 nitrogen and 1 oxygen or 1

sulphur ring atoms, optionally C-substituted by oxo, C₁-C₆ alkoxy-(C₁-C₆)-alkyl, amino-(C₁-C₆)-alkyl, fluoro-(C₁-C₆)-alkyl, fluoro-(C₁-C₆)-alkoxy, fluoro-(C₂-C₅)-alkanoyl, halo, cyano, -OR⁵, R⁶, -COR⁵, -NR⁵R⁵, -COOR⁵, -S(O)_mR⁶, -SO₂NR⁵R⁵, -CONR⁵R⁵, -NR⁵SO₂R⁶ or -NR⁵COR⁶ and optionally N-substituted
 5 by C₁-C₆ alkoxy-(C₁-C₆)-alkyl, amino-(C₂-C₆)-alkyl, fluoro-(C₁-C₆)-alkyl, fluoro-(C₂-C₅)-alkanoyl, R⁶, -COR⁵, -COOR⁵, -S(O)_mR⁶, -SO₂NR⁵R⁵ or -CONR⁵R⁵,
 or (iv) when A is C₂-C₃ alkylene, N-linked azetidiny, pyrrolidinyl, piperidinyl or piperazinyl, each being optionally C-substituted by C₁-C₆ alkyl, phenyl, C₁-C₆ alkoxy-(C₁-C₆)-alkyl, amino-(C₁-C₆)-alkyl, fluoro-(C₁-C₆)-alkyl, fluoro-(C₁-C₆)-alkoxy, C₂-C₅ alkanoyl, halo, -OR³, cyano, -COOR³, C₃-C₇ cycloalkyl, -S(O)_mR⁴,
 10 -NR³R³, -SO₂NR³R³, -CONR³R³, -NR³COR⁴ or -NR³SO₂R⁴ and optionally N-substituted by C₁-C₆ alkyl, phenyl, C₁-C₆ alkoxy-(C₁-C₆)-alkyl, amino-(C₂-C₆)-alkyl, fluoro-(C₁-C₆)-alkyl, C₂-C₅ alkanoyl, -COOR³, C₃-C₇ cycloalkyl, -S(O)_mR⁴, -SO₂NR³R³ or -CONR³R³;

15

R³ is H, C₁-C₆ alkyl or phenyl;

R⁴ is C₁-C₆ alkyl or phenyl;

20 R⁵ is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl, naphthyl or het;

R⁶ is C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl, naphthyl or het;

m is 0, 1 or 2; and

25

"het", used in the definitions of R⁵ and R⁶, means C-linked pyrrolyl, imidazolyl, triazolyl, thienyl, furyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, quinolinyl, isoquinolinyl, benzimidazolyl, quinazolinyl, phthalazinyl, benzoxazolyl or quinoxalinyl, each optionally
 30 substituted by C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano or halo.

3. A compound as claimed in claim 1 or claim 2 wherein A is a bond.

4. A compound as claimed in claim 1 or claim 2 wherein A is C₁-C₃ alkylene.
- 5 5. A compound as claimed in claim 1 wherein A is C₂-C₃ alkylene.
6. A compound as claimed in claim 5 wherein A is -CH₂CH₂-.
7. A compound as claimed in any one of the preceding claims wherein R² is
10 C₁-C₆ alkyl or phenyl.
8. A compound as claimed in claim 7 wherein R² is 2-methylprop-1-yl or phenyl.
- 15 9. A compound as claimed in claim 5 or claim 6 wherein R² is -NR⁷R⁸.
10. A compound as claimed in claim 9 wherein R⁷ is C₁-C₆ alkyl and R⁸ is C₃-C₈ cycloalkyl.
20
11. A compound as claimed in claim 10 wherein R⁷ is prop-2-yl and R⁸ is cyclopentyl.
12. A compound as claimed in any preceding claim wherein R¹ is C₁-C₆ alkyl
25 substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl.
13. A compound as claimed in claim 12 wherein R¹ is 2-phenylethyl, 2,2-diphenylethyl or 1-naphthylmethyl.
- 30
14. A compound as claimed in claim 1 wherein -A-R² is 2-[(2-propyl)(cyclopentyl)amino]ethyl, 2-methylprop-1-yl or phenyl.

15. A compound as claimed in claim 1 which is selected from the group consisting of:
- N*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-
5 [(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl)-2-methyl-1-propanesulfonamide;
- N*-[{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-(phenethylamino)-9*H*-purin-2-yl)methyl]benzenesulfonamide;
- N*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-
10 [(1-naphthylmethyl)amino]-9*H*-purin-2-yl)methyl]benzenesulfonamide; and
2-[cyclopentyl(isopropyl)amino]-*N*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl)ethanesulfonamide;
- and the pharmaceutically acceptable salts and solvates thereof.
- 15
16. A pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of the preceding claims, together with a pharmaceutically acceptable excipient, diluent or carrier.
- 20
17. A compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 15 and 16, respectively, for use as a medicament.
- 25
18. The use of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 15 and 16, respectively, for the manufacture of a medicament to treat a disease for which an A2a receptor agonist is indicated.
- 30
19. The use of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 15 and 16, respectively, for the manufacture of an anti-inflammatory agent.

20. The use of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 15 and 16, respectively, for the manufacture of a medicament for the treatment of a respiratory disease.

21. Use as claimed in claim 20 where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis.

22. The use of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 15 and 16, respectively, for the manufacture of a medicament for the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori*-gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing.

23. A method of treatment of a mammal, including a human being, to treat a disease for which an A2a receptor agonist is indicated, including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 15 and 16, respectively.

24. A method of treatment of a mammal, including a human being, to treat an inflammatory disease, including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable

salt, solvate or composition thereof, as claimed in any one of claims 1 to 15 and 16, respectively.

25. A method of treatment of a mammal, including a human being, to treat a
5 respiratory disease, including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 15 and 16, respectively.

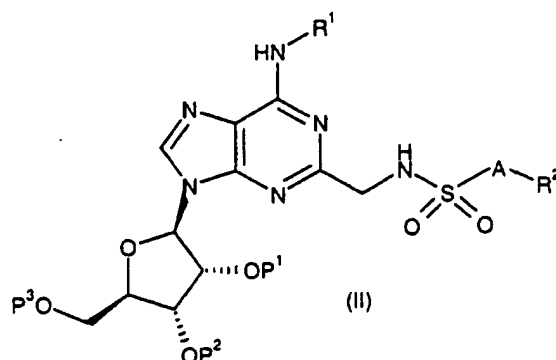
10 26. A method as claimed in claim 25 where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis.

15 27. A method of treatment of a mammal, including a human being, to treat septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease,
20 *Helicobacter pylori*-gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing, including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 15 and
25 16, respectively.

28. A process for the preparation of a compound of the formula (I), as claimed in claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate thereof, which includes

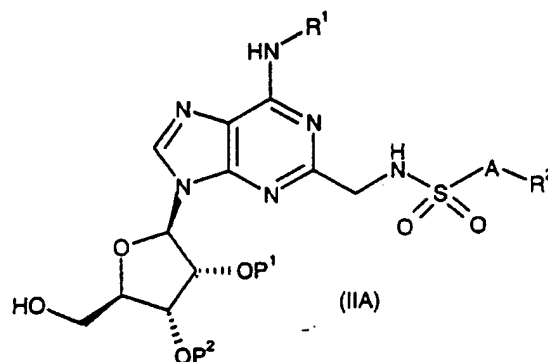
30

(a) deprotection of a compound of the formula



wherein R^1 , R^2 and A are as defined in claim 1 or claim 2 and either P^1 , P^2 and P^3 , when taken separately, are protecting groups or, P^1 and P^2 , when taken
 5 together are a protecting group and P^3 is a protecting group, the protecting groups being removed together or sequentially; or

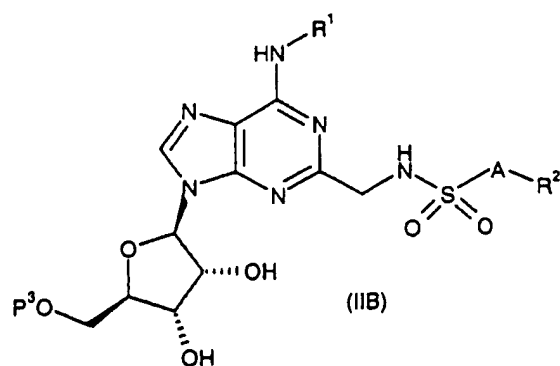
(b) deprotection of a compound of the formula



10

wherein R^1 , R^2 and A are as defined in claim 1 or claim 2 and either P^1 and P^2 , when taken separately, are protecting groups or, P^1 and P^2 , when taken together are a protecting group, the protecting groups P^1 and P^2 , when taken
 15 separately, being removed either together or sequentially; or

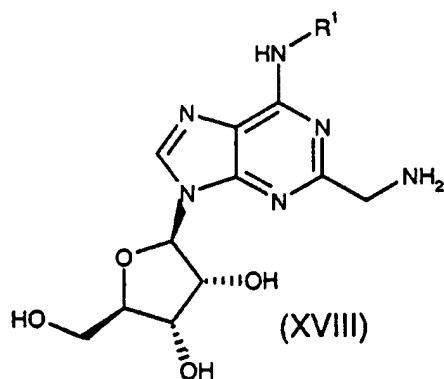
(c) deprotection of a compound of the formula



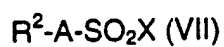
wherein P^3 is a protecting group and R^1 , R^2 and A are as defined in claim 1 or claim 2; or

5

(d) sulphonylation of a compound of the formula



10 wherein R^1 is as defined in claim 1 or claim 2, with a compound of the formula

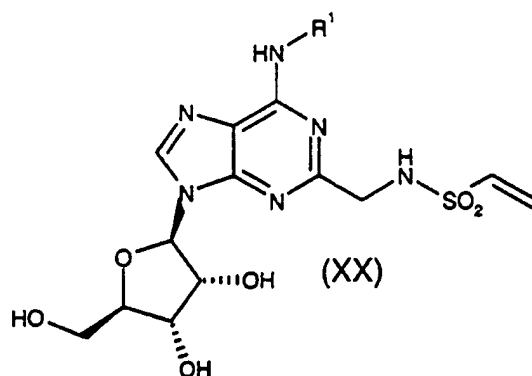


wherein X is a leaving group, preferably chloro and R^2 and A are as defined in

15 claim 1 or claim 2;

any one of said processes (a) to (d) being optionally followed by the conversion of the compound of the formula (I) to a pharmaceutically acceptable salt thereof.

- 5 29. A process for the preparation of a compound of the formula (I), as claimed in claim 1, in which A is $-\text{CH}_2\text{CH}_2-$ and R^2 is $-\text{NR}^7\text{R}^8$, or a pharmaceutically acceptable salt or solvate thereof, which includes the reaction of a compound of the formula



10

wherein R^1 is as defined in claim 1, with a compound of the formula



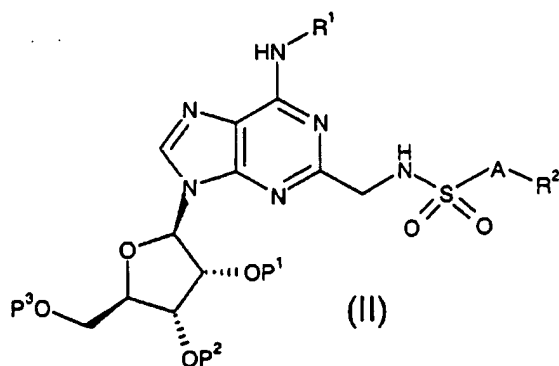
15

wherein R^7 and R^8 are as defined in claim 1;

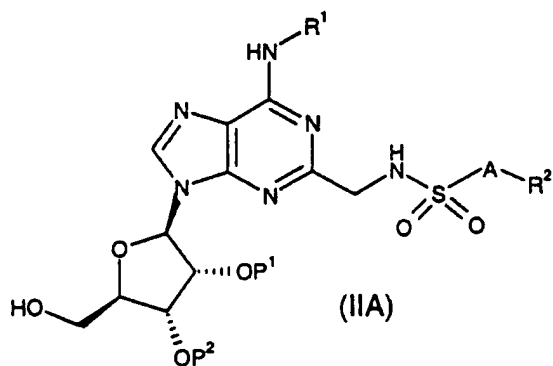
said process being optionally followed by the conversion of the compound of the formula (I) to a pharmaceutically acceptable salt thereof.

20

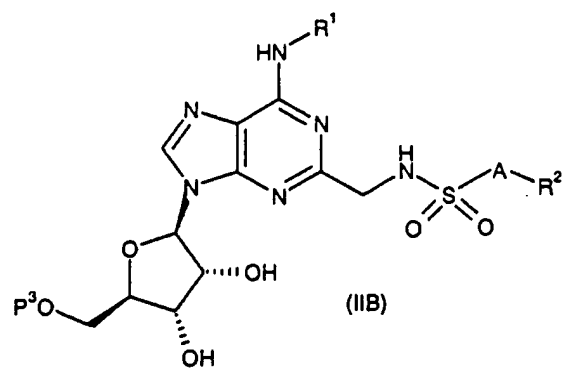
30. A compound of the formula



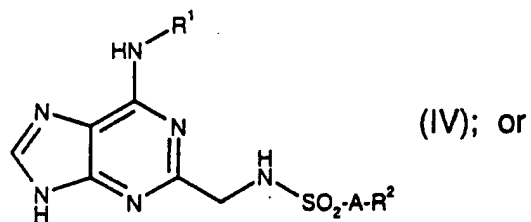
5 wherein either P^1 , P^2 and P^3 , when taken separately, are protecting groups or, P^1 and P^2 , when taken together are a protecting group and P^3 is a protecting group; or



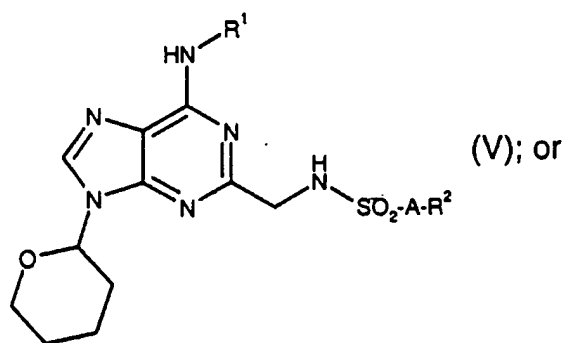
10 wherein either P^1 and P^2 , when taken separately, are protecting groups or, P^1 and P^2 , when taken together are a protecting group; or



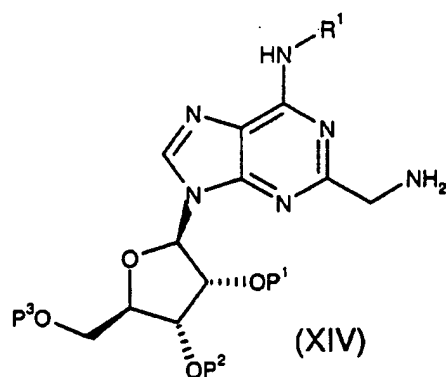
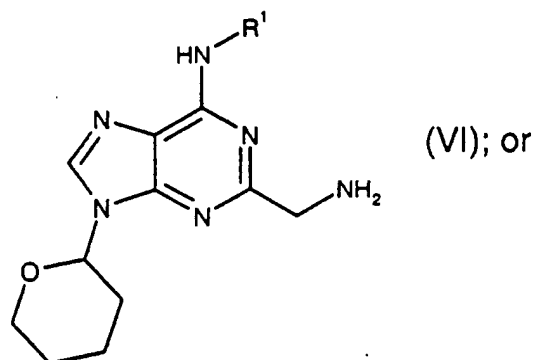
wherein P³ is a protecting group; or



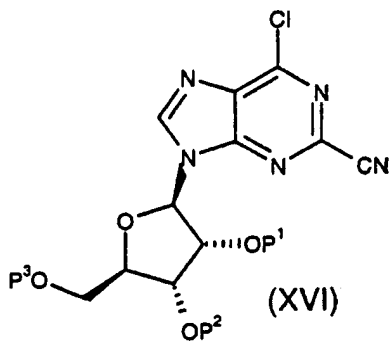
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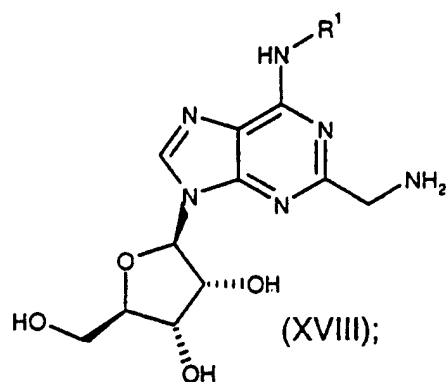
10



wherein either P^1 , P^2 and P^3 , when taken separately, are protecting groups or,
5 P^1 and P^2 , when taken together are a protecting group and P^3 is a protecting group; or



wherein either P^1 , P^2 and P^3 , when taken separately, are protecting groups or, P^1 and P^2 , when taken together are a protecting group and P^3 is a protecting group; or

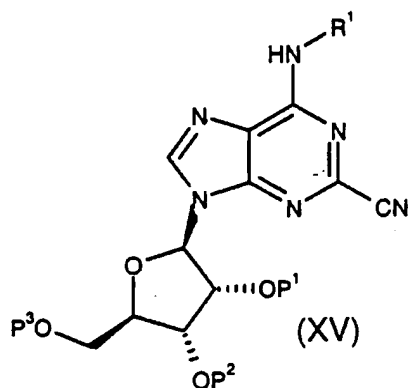


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the groups R^1 , R^2 and A being as defined in claim 1 or claim 2.

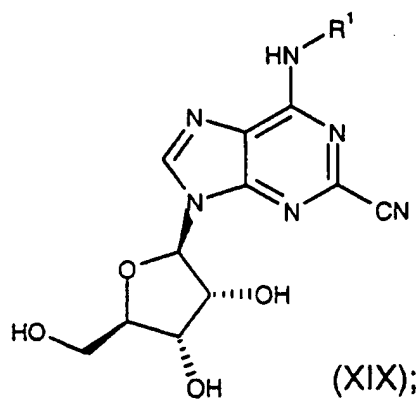
31. A compound of the formula

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wherein either P^1 , P^2 and P^3 , when taken separately, are protecting groups or, P^1 and P^2 , when taken together are a protecting group and P^3 is a protecting group; or

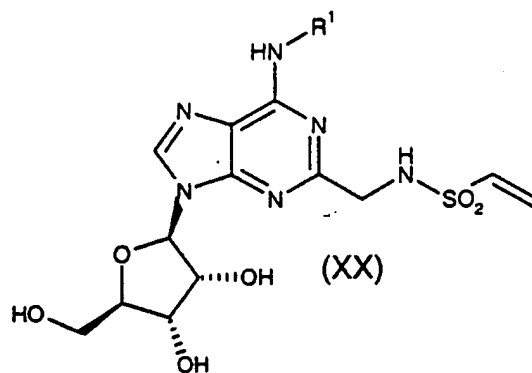
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the group R^1 being defined as C_1 - C_6 alkyl optionally substituted by 1 or 2
5 substituents each independently selected from phenyl and naphthyl, said
phenyl and naphthyl being optionally substituted by C_1 - C_6 alkyl, C_1 - C_6 alkoxy,
halo or cyano.

32. A compound of the formula

10



the group R^1 being as defined in claim 1.

15

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/01444

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H19/167 A61K31/70 A61P11/00 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, BIOSIS, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 877 180 A (LINDEN JOEL M ET AL) 2 March 1999 (1999-03-02) claim 1 ---	1,16-28, 30-32
A	WO 88 03147 A (WARNER LAMBERT CO) 5 May 1988 (1988-05-05) abstract ---	1,16-28, 30-32
A	E ONGINI ET AL: "Pharmacology of Adenosine A2A Receptors" TRENDS IN PHARMACOLOGICAL SCIENCES,GB,ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 17, no. 10, October 1996 (1996-10), pages 364-372, XP002123410 ISSN: 0165-6147 the whole document --- -/--	1,16-28, 30-32



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

29 January 2001

Date of mailing of the international search report

07/02/2001

Name and mailing address of the ISA

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Authorized officer

Scott, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/01444

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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